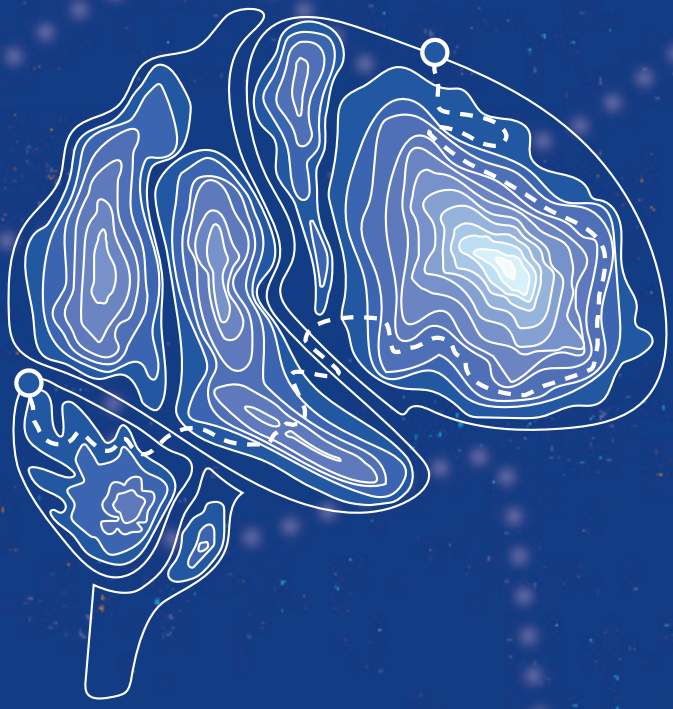
Electric Current and Emotional Control

Brain stimulation and mental health
in military personnel



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Fenne M. Smits

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Electric Current and Emotional Control

Brain stimulation and mental health in military personnel

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(met een samenvatting in het Nederlands)

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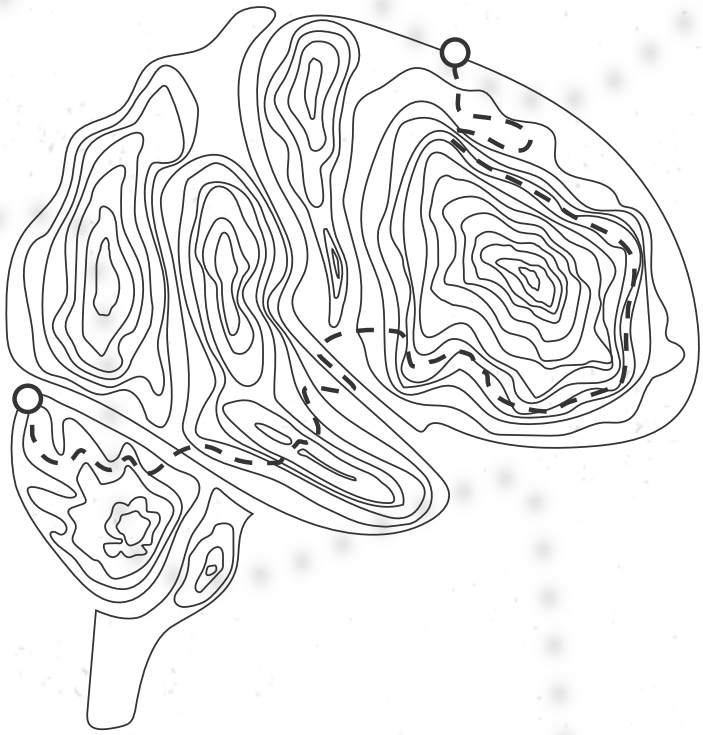


CHAPTER 1

| INTRODUCTION

"*What has been is what will be, and what has been done is what will be done; there is nothing new under the sun.***" – Ecclesiastes 1:9 (NRSV)**

Towards the end of the twentieth century, innovations in the field of brain stimulation elicited great interest by scientists and physicians in the field of neurology and psychiatry. Novel treatment possibilities were envisioned that could directly target pathological brain mechanisms in a feasible way. Yet, the practice of applying electrical currents to the human head was far from new. The ancient Romans already used electric torpedo fish to treat headaches[1].

In the 18th century, electricity was discovered to play a crucial role in the function and control of muscles and in the communication between the brain and the body[2]. This led to the development of the first devices that applied electrical currents to the head to influence electrical signals in the brain, initially with the aim to treat personality disorders[2]. Based on this work, 'shock therapy' (electroconvulsive therapy, ECT) was introduced in the 1930s for the treatment of schizophrenia and manias[3]. For ECT, electrical currents are applied to the scalp with intensities going up to 900 milli-Ampère (mA), inducing seizures. ECT has widespread biochemical effects in the brain, including increased release of several neurotransmitters (e.g., dopamine, serotonin) and neurohormones (e.g., endorphins, adrenocorticotropic hormone)[4]. Although the understanding of its mechanism of action is incomplete, ECT is still an effective psychiatric treatment today for conditions like severe depression[4]. More focal brain stimulation was made possible in the 1960s, when neurosurgeons started to implant stimulating electrodes into brain structures like the thalamus and hypothalamus in order to alleviate chronic pain and tremor in patients with Parkinson's disease[5,6]. Not much later, deep brain stimulation was also introduced in psychiatry, in particular to treat severe forms of depression, Tourette's syndrome, and obsessive-compulsive disorder[5].

ECT and deep brain stimulation are still used in psychiatry today, and their therapeutic effects may also provide opportunities for the treatment of stress- and anxiety-related mental health disorders (see Box 1.1.). However, these techniques carry the health risks that come along with brain surgery or epileptic seizures, and can additionally lead to significant side effects such as increased risk for cardiovascular disease and cognitive impairments[7,8]. It was therefore opportune when much safer possibilities for brain stimulation became available a few decades ago. Between the mid-1980s and 2000, it was shown that magnetic pulses or weak electrical currents administered from outside the head could also influence local brain activity[9–11]. The explosion of scientific publications on the topic since these findings illustrates the enthusiasm that emerged around these non-invasive brain stimulation techniques[12,13].

The potential of non-invasive brain stimulation as a psychiatric treatment tool was soon put forward. Already in the 1990s, case studies showed that transcranial magnetic stimulation (TMS) of the prefrontal cortex had therapeutic effects in depression, obsessive-compulsive

disorder and posttraumatic stress disorder (PTSD)[a14–16]. Relative to TMS, the therapeutic effects of the somewhat later developed transcranial electrical stimulation technique on stress-related disorders like anxiety and PTSD have been less studied[17,18].

Box 1.1. ECT and deep brain stimulation in stress-related disorders

Preliminary evidence suggests clinical potential of ECT and deep brain stimulation to treat anxiety and posttraumatic stress disorder (PTSD) symptoms. For example, some researchers have tried to use one of the well-known side effects of ECT, temporary memory loss[86], to disrupt traumatic memories[87], although this method has not yet yielded successful results in the treatment of PTSD[88]. Regarding deep brain stimulation, structures like the amygdala, hippocampus or ventral striatum are potentially effective stimulation targets[89,90]. Studies of deep brain stimulation in treatment-resistant PTSD patients are ongoing[91,92].

MILITARY STRESS AND MENTAL HEALTH RISKS

Exposure to stressful situations is inherent to military operations. Sources of stress include working under constant threat, extreme environments (e.g., heat, time pressure), witnessing severe suffering and risking physical injury or death[19,20]. Such stressors bring about a cascade of physiological and psychological effects that serve to effectively adapt to a situation and restore the body's homeostasis[21,22]. While stress is inevitable and serves an adaptive function, severe or chronic stress responses can have a maladaptive impact on health and military readiness. For example, during military operations, severe stress can narrow perception and attention (e.g., resulting in a tunnel vision that reduces situational awareness) and which can decrease the cognitive flexibility required for adequate decision-making and analysis in complex, uncertain and life-threatening situations[23,24]. Additionally, and most devastating on the long term, severe stress can be detrimental to physical and mental health. Stress- and anxiety-related mental health symptoms, for example, are characterized by trouble with controlling worries or intrusive traumatic memories, being easily upset or angry, feeling constantly "on edge" or hypervigilant, and suffering from sleeplessness. Indeed, it has been shown that military deployment increases the risk on pathological anxiety, hostility and posttraumatic stress disorder (PTSD)[25,26].

Treatment

Evidence-based treatments for stress-related mental health disorders include cognitive-behavioral psychotherapies[27,28]. One of the major aims of these therapies is to diminish distressing feelings and associated maladaptive actions and thoughts (e.g., "I was attacked in a forest, so wooded areas are dangerous.") by promoting alternative and more adaptive

a. At present, TMS over the left or right prefrontal cortex has shown level A evidence ('definite therapeutic efficacy') for depression. For PTSD, level B evidence ('probable therapeutic efficacy') is shown, and promising findings have been reported also for generalized anxiety disorder[84,85]

interpretations and beliefs of the feared event (e.g., "I was attacked in a forest, but many other wooded areas are safe places to be.")[29]. Additionally, effective pharmacotherapy is available to treat stress-related mental health symptoms, such as antidepressant and antipsychotic medication[30]. These pharmacotherapies are thought to target disbalances in neurobiological systems involved in anxiety and PTSD, such the noradrenergic, serotonergic, and glutamatergic systems[31]. However, the stress-attenuating effects of some pharmacotherapies can also hinder clinical effectivity of cognitive-behavioral psychotherapies that depend on fear memory-extinction methods[32].

Despite the availability of these evidence-based treatment options, military and veteran populations show a complex course of symptom development and their recovery estimates are poor. Clinical symptoms after military trauma may unfold over years or even decades[33], and almost half of military veterans with stress-related disorders like PTSD (30-55%) do not recover or continue to experience significant symptoms after treatment[34,35]. This illustrates the need for novel methods to ameliorate resilience to, and recovery of, stress-related mental health problems in this population.

THE BRAIN AND STRESS

The first response to a stressful event is preparing the body for action. The sympathetic nervous system releases adrenaline (epinephrine) and noradrenaline into the body's circulation and mobilizes mechanisms for "fight-flight-or-freeze", for example by accelerating heart rate[36–38]. Additionally, the hypothalamic-pituitary-adrenal axis (HPA-axis) releases glucocorticoid hormones to regulate the body's biological mechanisms to facilitate the stress response (e.g., reduce metabolic and immune system activities)[39].

In the brain, many regions respond and interact to promote survival in the face of danger, ensure storage of information for future stressful events, and allow adaptive adjustments and recovery of the stress response depending on the context. The amygdala is one of the key regions in the stress or survival circuit[40]; it is involved in detecting potential threats and other salient stimuli in the environment and can "ring the alarm bells" by initializing a stress response[41]. This is a reflexive and fast subcortical process, and has been compared to the principle of a smoke detector[42]. A slower but more reflective process involves interactions with other subcortical and cortical areas. For example, the perceived salient stimulus is evaluated with respect to its context and compared to prior experience, to determine if and to what extent it poses a real threat. For this process, the amygdala receives input from the ventromedial prefrontal cortex and the hippocampus (a key region in the memory circuit)[41,43,44]. In case of a "false alarm", the ventromedial prefrontal cortex can inhibit the amygdala[43]. The ventromedial prefrontal cortex is in turn connected to other parts of the prefrontal cortex that together guide our highest-order cognitive abilities and regulate our behavior. Broadly speaking, the ventral and medial parts of the prefrontal cortex regulate emotions, while the dorsal and lateral parts of the prefrontal cortex regulate attention, thoughts and actions[45] (see **Figure 1**).

Fundamentally, stress facilitates immediate survival as well as processes important for development, such as motivation and learning[40]. For instance, mild stress stimulates cells in the prefrontal cortex, promoting higher-order cognitive functions such as attention[46,47]. However, when stress levels are high (e.g., panic in response to an unescapable threat) and prolonged, the cognitive processes in the prefrontal cortex are tuned down in favor of the faster reflexive processes involving subcortical circuits (including the amygdala) that drive emotional and habitual behavior[48,49]. This can profoundly affect cognition and behavior of individuals in stressful situations (e.g., tunnel vision as mentioned above), including extensively trained soldiers[24,50].

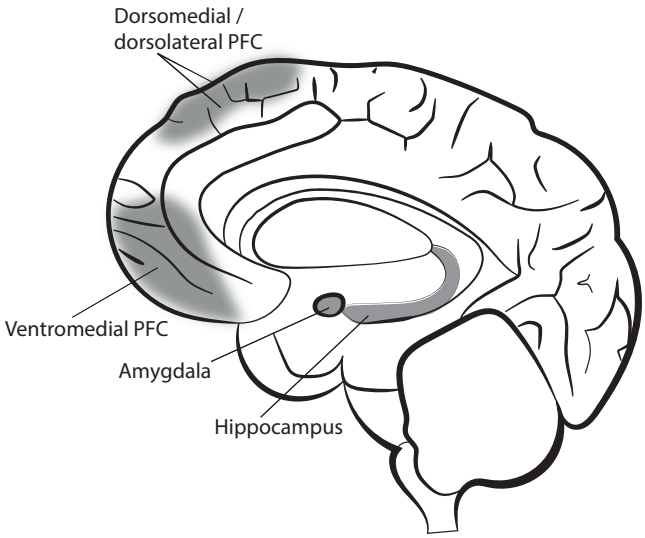


Figure 1. Schematic overview of some of the key brain regions involved in orchestrating the response to potential threats.

When does it go wrong?

When stress is excessive or becomes chronic, the stress response can be activated too frequently, fail to properly shut off after the threat has passed, or fail to dynamically adapt between stress and rest[21,51–55]. In addition, humans have the capacity to anticipate possible future threats. In pathological anxiety and PTSD, such anticipatory processes are biased towards excessive action preparation and excessive worrying in the face of uncertainty or unpredictable threats, which further elevates attention for threat, stress levels and the "alarm signaling" of the amygdala[56]. Additionally, threats are less well distinguished from safe situations, arguably due to a disrupted inhibitory connection between the ventromedial prefrontal cortex and the amygdala, hindering safety learning. At the same time, disrupted functioning of other areas in the prefrontal cortex (such as dorsolateral and ventrolateral parts) leads to exaggerated expectations of danger and avoidance behavior. Impaired activation of these areas has been associated with impaired emotion regulation and impaired executive

control functions such as attention deficits and impulsivity[44,56,57]. Hence, targeting activity in dorsolateral and ventrolateral prefrontal cortex regions may restore impairments in regulatory functions like emotion regulation and executive control and thereby support adaptive coping with stress.

NON-INVASIVE BRAIN STIMULATION

Non-invasive brain stimulation techniques provide opportunities to promote ventrolateral and dorsolateral prefrontal cortex activity. As introduced above, the two major non-invasive brain stimulation techniques that can target activity in superficial layers of the cortex are TMS and transcranial electrical stimulation. The present work almost entirely focuses on transcranial direct current stimulation (tDCS). Compared to TMS, tDCS has a better safety profile, is user-friendly, cheaper, and – importantly – portable[58]. Beside the economic advantages, these characteristics make tDCS much more suitable for scalable interventions that can be applied in the military context and in outpatient clinical care.

Mechanisms of action

TDCS uses weak direct currents (typically 1-2 milliamperes) that flow from a positive electrode (anode) to a negative electrode (cathode) placed on the scalp. Much of the electrical current is shunted by the scalp, but some electrical current penetrates the surface of the underlying cortex[59] where it leads to depolarization or hyperpolarization of the membrane of neural cell bodies, as graphically depicted **Figure 2**. This effect was reintroduced to modern scientific methods by experiments showing that the motor cortex could be polarized by applying weak direct currents to the head[9,60]. In a series of experiments[9], Nitsche and Paulus applied currents of 0.2-1 mA for 1-5 minutes between two scalp electrodes. Before and afterwards, excitability (i.e., firing probability) of the motor cortex was measured by assessing the motor-evoked potential (MEP) of the abductor digiti minimi hand muscle by administering a single TMS-pulse to the cortical motor neurons representing that hand muscle. TDCS with intensities higher than 0.6 mA and durations longer than 3 minutes were shown to significantly modulate the excitability of this central motor pathway. More specifically, anodal stimulation of the motor cortex increased excitability in the motor pathway as demonstrated by higher MEPs, while cathodal stimulation of the motor cortex decreased it. This effect was only found when one electrode was placed on a scalp location overlying the primary motor cortex, and the return electrode on the contralateral forehead (in contrast to a return electrode placed over, for example, the occipital cortex). In a later study, this stimulation-induced excitability change was shown to last for almost 1.5 hours when stimulation was continued for a longer period (9-13 minutes), the so-called after-effects of tDCS[61]. Since these initial reports, the effects of tDCS on motor cortex excitability have been replicated many times[62].

However, how do the weak currents of tDCS influence firing probability? Anodal tDCS causes membrane depolarizations that are well below the threshold for action potentials. The intensity of a tDCS-induced electric field in the cortex is typically lower than 1 Volt/meter[63]. At the level of a single neuron, this elicits an estimated membrane potential change

of approximately 0.2-0.5 mV[64]. Considering that membrane depolarizations to ~50 mV are needed to initiate an action potential, the effect of tDCS on single neurons is very small. Yet, slight changes in the resting membrane potential and associated firing probability in single neurons can generate changes in spontaneous neural firing rates that are amplified on the level of larger neural networks[64,65]. This likely drives the effect of tDCS on cortical excitability.

Furthermore, tDCS has been shown to modulate processes involved in synaptic plasticity[66–68]. Synaptic plasticity refers to the dynamic shaping of synaptic connections between neurons and is an important mechanism underlying learning and memory[69]. For example, the after-effects of tDCS on excitability were shown to be abolished by blocking the NMDA-receptor[68], suggesting that the after-effects of tDCS depend on long-term potentiation (LTP) and long-term depression (LTD) processes involved in synaptic plasticity. Furthermore, tDCS has been shown to affect levels of neurotransmitters that are involved in synaptic transmission: anodal stimulation reduces levels of GABA (involved in inhibitory synaptic transmission) and cathodal stimulation reduces levels of glutamate (involved in excitatory synaptic transmission), which is associated with the excitatory and inhibitory effects of anodal and cathodal stimulation respectively[66,70].

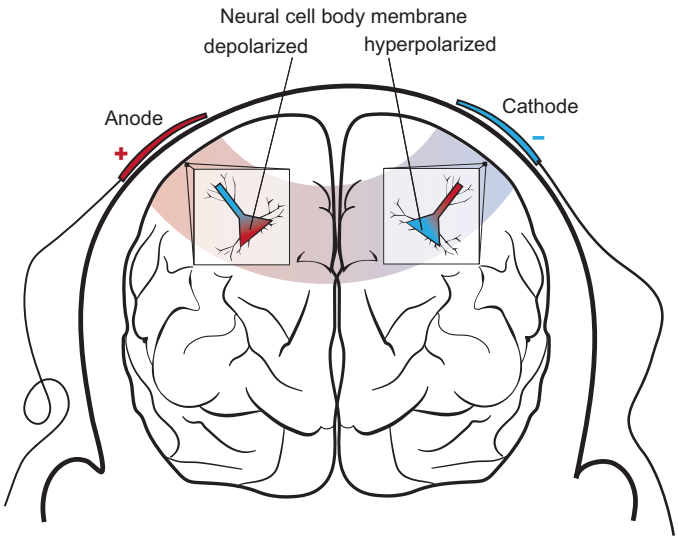


Figure 2. Model of tDCS effects on neural excitability under the anode *versus* cathode.

Translation to clinical applications

Clinical research with non-invasive brain stimulation in psychiatry has been ongoing for some years, although still in its early stages. When we started our studies, depression research dominated the field. Evidence for antidepressant effects of tDCS has reached level B ('probable efficacy') for anodal tDCS over the left dorsolateral prefrontal cortex, aimed at restoring the relative hypoactivity of this region observed in depression[71]. This tDCS protocol

additionally showed favorable effects on cognitive symptoms in patients with depression, such as improvements in (working) memory and in the regulation of cognitive interference of emotional information[71]. The effect of tDCS on such top-down cognitive control mechanisms could also be relevant to stress-related disorders like PTSD and anxiety. Anodal tDCS may help to restore the hypoactivity in the ventrolateral and dorsolateral parts of the prefrontal cortex that has been associated with impaired regulation of stress-related emotions such as anxiety and anger[72,73]. This effect could be mediated by cognitive functions that are involved in effective emotion regulation, including working memory and inhibitory control[74,75]. Following this rationale, anodal tDCS over the prefrontal cortex may be effective to alleviate stress-related symptoms by improving top-down control mechanisms.

However, evidence for clinical efficacy of tDCS in the domain of stress-related disorders has been scarce. At the time the research of this thesis was initiated, only one series of case studies in PTSD patients was published[76]. Saunders and coworkers described the effects of tDCS over the left prefrontal cortex in conjunction to computerized cognitive training in four male war veterans. While the authors reported improvements on cognitive and emotional performance measures (e.g., attention and empathy), insight in the clinical effectivity of tDCS on PTSD symptoms was limited. Empirical support for the idea that tDCS could improve top-down control of stress-related mechanisms came from laboratory studies in nonclinical populations. For example, anodal tDCS over the left dorsolateral prefrontal cortex was shown to reduce attentional bias for threat[77], attenuate physiological reactivity to stressors[78], and improve frustration tolerance[79]. Although such results were promising, these studies were typically performed with limited sample sizes. Moreover, randomized controlled tDCS trials in patients with anxiety, aggression regulation problems or PTSD were lacking[17,80]. Hence, to gain better insight in the clinical efficacy of tDCS for stress-related mental health disorders, larger-scale trials in relevant clinical populations with appropriate sample sizes are needed.

STUDY AIMS AND OUTLINE

The present work was therefore aimed at translating laboratory tDCS research to a clinically relevant population in well-powered studies. The overarching hypothesis was that treatment and resilience for stress-related mental health symptoms in the military could be improved by boosting functioning of regions in the lateral prefrontal cortex using anodal tDCS.

The objective of our first study was to gain more insight in the effectivity and optimal stimulation parameters of non-invasive brain stimulation to affect processes relevant to stress resilience and recovery. In addition to tDCS studies, we also included studies of repetitive TMS (rTMS). TMS uses magnetic pulses that induce an electric field of short duration (~0.5 ms) in the underlying cortex, where it is strong enough to initiate action potentials (peak intensities around 100 V/m)[11,81]. Repetitive trains of magnetic pulses applied in a low frequency (<1 Hz) inhibit cortical excitability and synaptic plasticity, while a high frequency (5-20 Hz) enhances it[82,83]. These rTMS protocols are often used with similar aims as cathodal and anodal tDCS, that is, to inhibit or facilitate activity in the targeted cortical region. **Chapter 2**

describes a systematic review and meta-analysis of experimental studies of rTMS or tDCS of the prefrontal cortex. The effects of rTMS and tDCS on emotion regulation were quantified based on changes in emotional responses to (laboratory) stressors. The influence of several stimulation parameters, such as targeted hemisphere (left vs. right prefrontal cortex) and polarity (anodal vs. cathodal tDCS) were additionally evaluated.

Box 1.2. Functional targeting with tDCS

One widely adopted theoretical framework suggesting state-dependency of tDCS-effects is the 'activity-selective hypothesis'[93]. According to this hypothesis, the subthreshold effect of tDCS by itself is relatively weak and unspecific, but when added to an activated neural pathway, it can significantly modulate the already ongoing neural activity and synaptic potentiation. Empirical support for this hypothesis comes, for example, from *in vitro* studies showing that anodal direct current stimulation enhances synaptic plasticity in hippocampal slices when plasticity is concurrently induced, but not when synapses are only weakly activated[67,94]. Likewise, meta-analytic results of *in vivo* studies showed significantly stronger effects on cognitive performance when anodal tDCS is applied during cognitive learning (which induces synaptic plasticity) than during cognitive test-performance[95]. Moreover, in a study of verbal fluency task performance[96], anodal tDCS over the left inferior frontal gyrus has been shown to enhance TMS-evoked responses in EEG (representing cortical excitability) when a TMS pulse was applied to another verbal fluency-related region (left premotor cortex), but not when the TMS pulse was applied to a task-unrelated region (superior parietal lobule). This suggest that tDCS predominantly modulates excitability and *ongoing* plasticity in cortical regions that are activated during stimulation.

Importantly, the activity-selective hypothesis makes two predictions that are relevant to the present work. First, tDCS combined with a learning task that induces synaptic plasticity would yield stronger effects. Second, the effects of tDCS would be specific to the domain of the learning task. This has also been called 'functional targeting' with tDCS.

Next, **Chapter 3** and **Chapter 4** describe a tDCS study in a military patient sample with PTSD, anxiety and aggression regulation problems. An intervention was applied with five sessions of tDCS over the right ventrolateral prefrontal cortex (inferior frontal gyrus) combined with computerized cognitive training, based on evidence suggesting that tDCS effectivity is higher when the stimulation is combined with a learning task, see Box 1.2. The combined tDCS-training intervention was hypothesized to recover stress-related impairments in inhibitory control, and in turn improve symptom recovery. **Chapter 3** presents a large randomized controlled trial (RCT) on the effectivity of this intervention. In addition, because successful implementation of potential novel treatment tools like tDCS also depend on its acceptability for the end users in clinical practice, **Chapter 4** describes a mixed-method study on the

experience and perspectives of military patients and caregivers on the acceptability of tDCS in the treatment of stress-related mental health disorders.

Chapter 5 and **Chapter 6** describe a second tDCS study on the effect of combined tDCS and cognitive training to boost psychological resilience in healthy military personnel. **Chapter 5** presents the study of the main hypothesis that this tDCS-training intervention would enhance emotional working memory, and in turn improve top-down stress regulation capacities. **Chapter 6** presents the study of the secondary outcomes of this study which involve cognitive changes (inhibitory and attentional control) and neural activity changes (EEG-based event-related potentials and frontal activity asymmetry) associated with the tDCS-training intervention.

The general discussion of **Chapter 7** summarizes the study results and conclusions. This chapter also critically evaluates the methods and observed results of the present work. This is followed by suggested directions for future research. Finally, the clinical implications and ethical considerations related to the studies of this thesis are considered.

REFERENCES

1. Kellaway P. Electric Fish and the Discovery of Animal Electricity: The mystery of the electric fish motivated research into electricity and was instrumental in the emergence of electrophysiology. *Bulletin of the History of Medicine*. 1946;20(2):112-137. Accessed March 8, 2022. https://www.jstor.org/stable/27852970?seq=1#metadata_info_tab_contents

2. Parent A. Giovanni Aldini: From Animal Electricity to Human Brain Stimulation. *THE CANADIAN JOURNALOF NEUROLOGICALSCIENCES*. 2004;31:576-584. doi:10.1017/S0317167100003851

3. Abrams R. *Electroconvulsive Therapy.* Oxford University Press; 1988. Accessed March 8, 2022. https://psycnet.apa.org/record/1988-98038-000

4. Kellner CH, Greenberg RM, Murrough JW, Bryson EO, Briggs MC, Pasculli RM. ECT in Treatment-Resistant Depression. *American Journal of Psychiatry*. 2012;169(12):1238-1244. doi:10.1176/appi.ajp.2012.12050648

5. Kringelbach ML, Jenkinson N, Owen SLF, Aziz TZ. Translational principles of deep brain stimulation. *Nature Reviews Neuroscience 2007 8:8*. 2007;8(8):623-635. doi:10.1038/nrn2196

6. Perlmutter JS, Mink JW. DEEP BRAIN STIMULATION. *http://dx.doi.org/101146/annurev.neuro29051605112824*. 2006;29:229-257. doi:10.1146/ANNUREV.NEURO.29.051605.112824

7. Witt K, Daniels C, Volkmann J. Factors associated with neuropsychiatric side effects after STN-DBS in Parkinson's disease. *Parkinsonism and Related Disorders*. 2012;18(SUPPL. 1):168-170. doi:10.1016/S1353-8020(11)70052-9

8. Datto CJ, in Geri- I. SIDE EFFECTS OF ELECTROCONVULSIVE THERAPY. *DEPRESSION AND ANXIETY*. 2000;12:130-134. doi:10.1002/1520-6394

9. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *The Journal of Physiology*. 2000;527(3):633-639. doi:10.1111/j.1469-7793.2000.t01-1-00633.x

10. Pascual-leone A, Valls-solé J, Wassermann EM, Hallett M. Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. *Brain*. 1994;117(4):847-858. doi:10.1093/BRAIN/117.4.847

11. Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. *Lancet*. 1985;1(8437):1106-1107. doi:10.1016/S0140-6736(85)92413-4

12. Polanía R, Nitsche MA, Ruff CC. Establishing brain-behavior relations with NIBS Studying and modifying brain function with non-invasive brain stimulation. *Nature Neuroscience*. 2018;21:174-187. doi:10.1038/s41593-017-0054-4

13. Fecteau S. Influencing Human Behavior with Noninvasive Brain Stimulation: Direct Human Brain Manipulation Revisited: *https://doi.org/101177/10738584211067744*. Published online January 20, 2022. doi:10.1177/10738584211067744

14. Grisaru N, Amir M, Cohen H, Kaplan Z. Effect of transcranial magnetic stimulation in posttraumatic stress disorder: a preliminary study. *Biol Psychiatry*. 1998;44(1):52-55. doi:10.1016/S0006-3223(98)00016-X

15. McCann UD, Kimbrell TA, Morgan CM, et al. Repetitive transcranial magnetic stimulation for posttraumatic stress disorder. *Arch Gen Psychiatry*. 1998;55(3):276-279. doi:10.1001/ARCHPSYC.55.3.276

16. George MS, Wassermann EM, Post RM. Transcranial magnetic stimulation: A neuropsychiatric tool for the 21st century. *Journal of Neuropsychiatry and Clinical Neurosciences*. 1996;8(4):373-382. doi:10.1176/JNP.8.4.373

17. Vicario CM, Salehinejad MA, Felmingham K, Martino G, Nitsche MA. A systematic review on the therapeutic effectiveness of non-invasive brain stimulation for the treatment of anxiety disorders. *Neuroscience and Biobehavioral Reviews*. 2019;96(August 2018):219-231. doi:10.1016/j.neubiorev.2018.12.012

18. Gouveia FV, Davidson B, Meng Y, et al. Treating Post-traumatic Stress Disorder with Neuromodulation Therapies: Transcranial Magnetic Stimulation, Transcranial Direct Current Stimulation, and Deep Brain Stimulation. *Neurotherapeutics*. 2020;17(4):1747-1756. doi:10.1007/S13311-020-00871-0/TABLES/3

19. Reijnen A, Rademaker AR, Vermetten E, Geuze E. Prevalence of mental health symptoms in Dutch military personnel returning from deployment to Afghanistan: A 2-year longitudinal analysis. *Eur Psychiatry*. Published online 2014:6-11. doi:10.1016/j.eurpsy.2014.05.003

20. Bartone PT, Adler AB, Vaitkus MA. Dimensions of Psychological Stress in Peacekeeping Operations. *Military Medicine*. 1998;163(9):587-593. doi:10.1093/milmed/163.9.587

21. McEwen BS. Stress, Adaptation, and Disease: Allostasis and Allostatic Load. *Ann N Y Acad Sci*. 1998;840(1):33-44. doi:10.1111/j.1749-6632.1998.tb09546.x

22. Selye H. What is stress? *Metabolism*. 1956;5(5):525-530. Accessed April 14, 2022. http://www.ncbi.nlm.nih.gov/pubmed/13358567

23. Kavanagh J. Stress and Performance A Review of the Literature and Its Applicability to the Military. Published online 2005. Accessed August 31, 2021. http://www.rand.org/

24. Martin K, McLeod E, Périard J, Rattray B, Keegan R, Pyne DB. The Impact of Environmental Stress on Cognitive Performance: A Systematic Review. *Human Factors: The Journal of the Human Factors and Ergonomics Society*. 2019;61(8):1205-1246. doi:10.1177/0018720819839817

25. van der Wal SJ, Geuze E, Vermetten E. Long-term risk for mental health symptoms in Dutch ISAF veterans: the role of perceived social support. *Psychological Medicine*. Published online January 18, 2022:1-11. doi:10.1017/S0033291721005389

26. Sareen J, Cox BJ, Afifi TO, et al. Combat and peacekeeping operations in relation to prevalence of mental disorders and perceived need for mental health care: findings from a large representative sample of military personnel. *Arch Gen Psychiatry*. 2007;64(7):843-852. doi:10.1001/archpsyc.64.7.843

27. Hamblen JL, Schnurr PP, Rosenberg A, Eftekhari A. A guide to the literature on psychotherapy for PTSD. *Psychiatric Annals*. 2009;39(6):348-354. doi:10.3928/00485713-20090515-02

28. Kitchiner NJ, Lewis C, Roberts NP, Bisson JI. Active duty and ex-serving military personnel with post-traumatic stress disorder treated with psychological therapies: systematic review and meta-analysis. *https://doi.org/101080/20008198.2019.1684226*. 2019;10(1). doi:10.1080/20008198.2019.1684226

29. Curtiss JE, Levine DS, Ander I, Baker AW. Cognitive-Behavioral Treatments for Anxiety and Stress-Related Disorders. *https://doi.org/101176/appi.focus20200045*. 2021;19(2):184-189. doi:10.1176/APPI.FOCUS.20200045

30. Watts B v., Schnurr PP, Mayo L, Young-Xu Y, Weeks WB, Friedman MJ. Meta-Analysis of the Efficacy of Treatments for Posttraumatic Stress Disorder. *The Journal of Clinical Psychiatry*. 2013;74(6):11710. doi:10.4088/JCP.12R08225

31. Ravindran LN, Stein MB. Pharmacotherapy of PTSD: Premises, principles, and priorities. *Brain Research*. 2009;1293:24-39. doi:10.1016/J.BRAINRES.2009.03.037

32. Otto MW, McHugh RK, Kantak KM. Combined pharmacotherapy and cognitive-behavioral therapy for anxiety disorders: Medication effects, glucocorticoids, and attenuated treatment outcomes. *Clinical Psychology: Science and Practice*. 2010;17(2):91-103. doi:10.1111/J.1468-2850.2010.01198.X

33. van der Wal SJ, Vermetten E, Elbert G. Long-term development of post-traumatic stress symptoms and associated risk factors in military service members deployed to Afghanistan: Results from the PRISMO 10-year follow-up. *European Psychiatry*. 2021;64(1):e10. doi:10.1192/j.eurpsy.2020.113

34. Haagen JFG, Smid GE, Knipscheer JW, Kleber RJ. The efficacy of recommended treatments for veterans with PTSD: A metaregression analysis. *Clinical Psychology Review*. 2015;40:184-194. doi:10.1016/j.cpr.2015.06.008

35. Bradley R, Greene J, Russ E, Dutra L, Westen D. A Multidimensional Meta-Analysis of Psychotherapy for PTSD. *American Journal of Psychiatry*. 2005;162(2):214-227. doi:10.1176/appi.ajp.162.2.214

36. Kvetnansky R, Sabban EL, Palkovits M. Catecholaminergic systems in stress: structural and molecular genetic approaches. *Physiol Rev*. 2009;89(2):535-606. doi:10.1152/physrev.00042.2006

37. LeDoux JE. Emotion Circuits in the Brain. *http://dx.doi.org/101146/annurev.neuro231155*. 2003;23:155-184. doi:10.1146/ANNUREV.NEURO.23.1.155

38. Hagenaars MA, Oitzl M, Roelofs K. Updating freeze: Aligning animal and human research. *Neuroscience & Biobehavioral Reviews*. 2014;47:165-176. doi:10.1016/J.NEUBIOREV.2014.07.021

39. Herman JP, Cullinan WE. Neurocircuitry of stress: Central control of the hypothalamo-pituitary-adrenocortical axis. *Trends in Neurosciences*. 1997;20(2):78-84. doi:10.1016/S0166-2236(96)10069-2

40. LeDoux J. Rethinking the Emotional Brain. *Neuron*. 2012;73(4):653-676. doi:10.1016/J.NEURON.2012.02.004

41. Shin LM, Liberzon I. The neurocircuitry of fear, stress, and anxiety disorders. *Neuropsychopharmacology*. 2010;35(1):169-191. doi:10.1038/npp.2009.83

42. Nesse RM. *The Smoke Detector Principle Natural Selection and the Regulation of Defensive Responses*.

43. VanElzakker MB, Kathryn Dahlgren M, Caroline Davis F, Dubois S, Shin LM. From Pavlov to PTSD: The extinction of conditioned fear in rodents, humans, and anxiety disorders. *Neurobiology of Learning and Memory*. 2014;113:3-18. doi:10.1016/j.nlm.2013.11.014

44. Milad MR, Wright CI, Orr SP, Pitman RK, Quirk GJ, Rauch SL. Recall of Fear Extinction in Humans Activates the Ventromedial Prefrontal Cortex and Hippocampus in Concert. *Biological Psychiatry*. 2007;62(5):446-454. doi:10.1016/j.biopsych.2006.10.011

45. Arnsten AFT. Stress signalling pathways that impair prefrontal cortex structure and function. *Nature Reviews Neuroscience*. 2009;10(6):410-422. doi:10.1038/nrn2648

46. Hadar R, Edemann-Callesen H, Hlusicka EB, et al. Recurrent stress across life may improve cognitive performance in individual rats, suggesting the induction of resilience. *Translational Psychiatry*. 2019;9(1). doi:10.1038/S41398-019-0523-5

47. Plieger T, Reuter M. Stress & executive functioning: A review considering moderating factors. *Neurobiology of Learning and Memory*. 2020;173:107254. doi:10.1016/J.NLM.2020.107254

48. Shields GS, Sazma MA, Yonelinas AP. The effects of acute stress on core executive functions: A meta-analysis and comparison with cortisol. *Neuroscience & Biobehavioral Reviews*. 2016;68:651-668. doi:10.1016/j.neubiorev.2016.06.038

49. Arnsten AFT. Stress weakens prefrontal networks: molecular insults to higher cognition. *Nature Neuroscience*. 2015;18(10):1376-1385. doi:10.1038/nn.4087

50. Morgan CA, Doran A, Steffian G, Hazlett G, Southwick SM. Stress-Induced Deficits in Working Memory and Visuo-Constructive Abilities in Special Operations Soldiers. *Biological Psychiatry*. 2006;60(7):722-729. doi:10.1016/J.BIOPSYCH.2006.04.021

51. Morris MC, Hellman N, Abelson JL, Rao U. Cortisol, heart rate, and blood pressure as early markers of PTSD risk: A systematic review and meta-analysis. *Clinical Psychology Review*. 2016;49:79-91. doi:10.1016/j.cpr.2016.09.001

52. Zoladz PR, Diamond DM. Current status on behavioral and biological markers of PTSD: A search for clarity in a conflicting literature. *Neuroscience and Biobehavioral Reviews*. 2013;37(5):860-895. doi:10.1016/j.neubiorev.2013.03.024

53. Belda X, Fuentes S, Daviu N, Nadal R, Armario A. Stress-induced sensitization: The hypothalamic-pituitary-adrenal axis and beyond. *Stress*. 2015;18(3):269-279. doi:10.3109/10253890.2015.1067678

54. de Kloet CS, Vermetten E, Geuze E, Kavelaars A, Heijnen CJ, Westenberg HGM. Assessment of HPA-axis function in posttraumatic stress disorder: Pharmacological and non-pharmacological challenge tests, a review. *Journal of Psychiatric Research*. 2006;40(6):550-567. doi:10.1016/j.jpsychires.2005.08.002

55. Meewisse ML, Reitsma JB, de Vries GJ, Gersons BPR, Olff M. Cortisol and post-traumatic stress disorder in adults: systematic review and meta-analysis. *Br J Psychiatry*. 2007;191(5):387-392. doi:10.1192/bjp.bp.106.024877

56. Grupe DW, Nitschke JB. Uncertainty and anticipation in anxiety: an integrated neurobiological and psychological perspective. *Nature Reviews Neuroscience*. 2013;14(7):488-501. doi:10.1038/nrn3524

57. Sheynin J, Liberzon I. Circuit dysregulation and circuit-based treatments in posttraumatic stress disorder. *Neuroscience Letters*. 2017;649:133-138. doi:10.1016/j.neulet.2016.11.014

58. Priori A, Hallett M, Rothwell JC. Repetitive transcranial magnetic stimulation or transcranial direct current stimulation? *Brain Stimulation*. 2009;2(4):241-245. doi:10.1016/j.brs.2009.02.004

59. Miranda PC, Lomarev M, Hallett M. Modeling the current distribution during transcranial direct current stimulation. *Clinical Neurophysiology*. 2006;117(7):1623-1629. doi:10.1016/J.CLINPH.2006.04.009

60. Priori A, Berardelli A, Rona S, Accornero N, Manfredi M. Polarization of the human motor cortex through the scalp. *Neuroreport*. 1998;9(10):2257-2260. doi:10.1097/00001756-199807130-00020

61. Nitsche MA, Paulus W. Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. *Neurology*. 2001;57(10):1899-1901. doi:10.1212/WNL.57.10.1899

62. Bastani A, Jaberzadeh S. Does anodal transcranial direct current stimulation enhance excitability of the motor cortex and motor function in healthy individuals and subjects with stroke: a systematic review and meta-analysis. *Clin Neurophysiol*. Published online 2012. doi:10.1016/j.clinph.2011.08.029

63. Woods AJ, Antal A, Bikson M, et al. A technical guide to tDCS, and related non-invasive brain stimulation tools. *Clinical Neurophysiology*. Published online 2016. doi:10.1016/j.clinph.2015.11.012

64. Stagg CJ, Antal A, Nitsche MA. Physiology of Transcranial Direct Current Stimulation. *Journal of ECT*. 2018;34(3):144-152. doi:10.1097/YCT.0000000000000510

65. Bikson M, Paulus W, Esmaeilpour Z, Kronberg G, Nitsche MA. Mechanisms of Acute and After Effects of Transcranial Direct Current Stimulation. *Practical Guide to Transcranial Direct Current Stimulation*. Published online 2019:81-113. doi:10.1007/978-3-319-95948-1_3

66. Cirillo G, di Pino G, Capone F, et al. Neurobiological after-effects of non-invasive brain stimulation. *Brain Stimulation*. 2017;10(1):1-18. doi:10.1016/j.brs.2016.11.009

67. Kronberg G, Bridi M, Abel T, Bikson M, Parra LC. Direct Current Stimulation Modulates LTP and LTD: Activity Dependence and Dendritic Effects. *Brain Stimulation*. 2017;10(1):51-58. doi:10.1016/j.brs.2016.10.001

68. Liebetanz D. Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability. *Brain*. 2002;125(10):2238-2247. doi:10.1093/brain/awf238

69. Malenka RC, Bear MF. LTP and LTD: An embarrassment of riches. *Neuron*. 2004;44(1):5-21. doi:10.1016/j.neuron.2004.09.012

70. Stagg CJ, Best JG, Stephenson MC, et al. Polarity-Sensitive Modulation of Cortical Neurotransmitters by Transcranial Stimulation. *Journal of Neuroscience*. 2009;29(16):5202-5206. doi:10.1523/JNEUROSCI.4432-08.2009

71. Lefaucheur JP, Antal A, Ayache SS, et al. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). *Clinical Neurophysiology*. 2017;128(1):56-92. doi:10.1016/j.clinph.2016.10.087

72. Hayes JP, Hayes SM, Mikedis AM. Quantitative meta-analysis of neural activity in posttraumatic stress disorder. *Biology of Mood & Anxiety Disorders*. 2012;2(1):9. doi:10.1186/2045-5380-2-9

73. Picó-Pérez M, Radua J, Steward T, Menchón JM, Soriano-Mas C. Emotion regulation in mood and anxiety disorders: A meta-analysis of fMRI cognitive reappraisal studies. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2017;79:96-104. doi:10.1016/J.PNPBP.2017.06.001

74. Kohn N, Eickhoff SB, Scheller M, Laird AR, Fox PT, Habel U. Neural network of cognitive emotion regulation — An ALE meta-analysis and MACM analysis. *Neuroimage*. 2014;87:345-355. doi:10.1016/j.neuroimage.2013.11.001

75. Webb TL, Miles E, Sheeran P. Dealing with feeling: A meta-analysis of the effectiveness of strategies derived from the process model of emotion regulation. *Psychological Bulletin*. 2012;138(4):775-808. doi:10.1037/A0027600

76. Saunders N, Downham R, Turman B, et al. Working memory training with tDCS improves behavioral and neurophysiological symptoms in pilot group with post-traumatic stress disorder (PTSD) and with poor working memory. *Neurocase*. 2015;21(3):271-278. doi:10.1080/13554794.2014.890727

77. Heeren A, Baeken C, Vanderhasselt MA, Philippot P, de Raedt R. Impact of Anodal and Cathodal Transcranial Direct Current Stimulation over the Left Dorsolateral Prefrontal Cortex during Attention Bias Modification: An Eye-Tracking Study. Hills PJ, ed. *PLOS ONE*. 2015;10(4):e0124182. doi:10.1371/journal.pone.0124182

78. Brunoni AR, Vanderhasselt MA, Boggio PS, et al. Polarity- and valence-dependent effects of prefrontal transcranial direct current stimulation on heart rate variability and salivary cortisol. *Psychoneuroendocrinology*. 2013;38(1):58-66. doi:10.1016/j.psyneuen.2012.04.020

79. Plewnia C, Schroeder PA, Kunze R, Faehling F, Wolkenstein L. Keep calm and carry on: improved frustration tolerance and processing speed by transcranial direct current stimulation (tDCS). Ward LM, ed. *PLoS One*. 2015;10(4):e0122578. doi:10.1371/journal.pone.0122578

80. Hampstead BM, Briceño EM, Mascaro N, Mourdoukoutas A, Bikson M. Current Status of Transcranial Direct Current Stimulation in Posttraumatic Stress and Other Anxiety Disorders. *Current Behavioral Neuroscience Reports*. Published online 2016. doi:10.1007/s40473-016-0070-9

81. Salinas FS, Lancaster JL, Fox PT. Detailed 3D models of the induced electric field of transcranial magnetic stimulation coils. *Physics in Medicine and Biology*. 2007;52(10). doi:10.1088/0031-9155/52/10/016

82. Pascual-Leone A, Tormos JM, Keenan J, Tarazona F, Cañete C, Catalá MD. Study and modulation of human cortical excitability with transcranial magnetic stimulation. *J Clin Neurophysiol*. 1998;15(4):333-343. doi:10.1097/00004691-199807000-00005

83. Hoogendam JM, Ramakers GMJ, di Lazzaro V. Physiology of repetitive transcranial magnetic stimulation of the human brain. *Brain Stimulation*. 2010;3(2):95-118. doi:10.1016/J.BRS.2009.10.005

84. Lefaucheur JP, Aleman A, Baeken C, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014–2018). *Clinical Neurophysiology*. 2020;131(2):474-528. doi:10.1016/J.CLINPH.2019.11.002

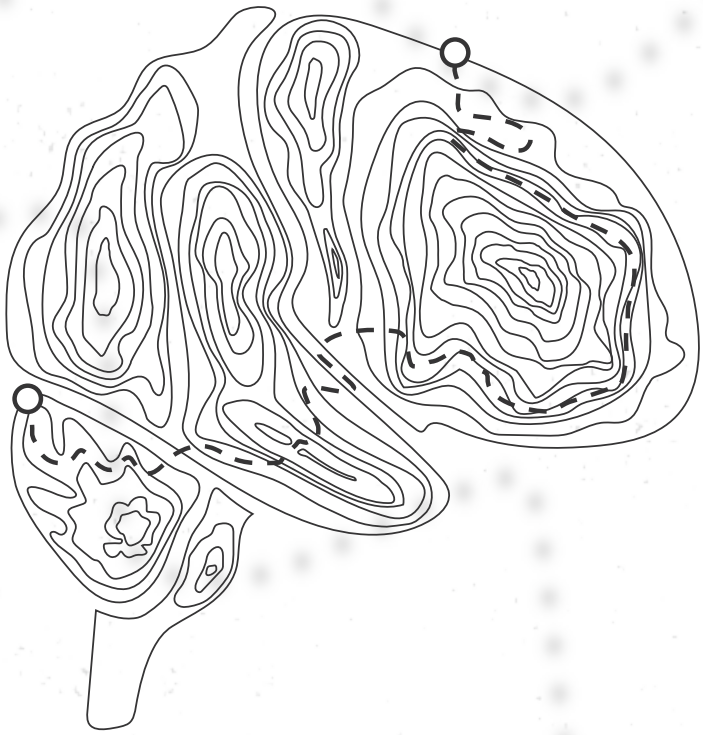
85. Cirillo P, Gold AK, Nardi AE, et al. Transcranial magnetic stimulation in anxiety and trauma-related disorders: A systematic review and meta-analysis. *Brain and Behavior*. 2019;9(6). doi:10.1002/brb3.1284

86. Bikson M, Rahman A. Origins of specificity during tDCS: anatomical, activity-selective, and input-bias mechanisms. *Frontiers in Human Neuroscience*. 2013;0(OCT):688. doi:10.3389/FNHUM.2013.00688

87. Kronberg G, Rahman A, Sharma M, Bikson M, Parra LC. Direct current stimulation boosts hebbian plasticity in vitro. *Brain Stimulation*. 2020;13(2):287-301. doi:10.1016/j.brs.2019.10.014

88. Simonsmeier BA, Grabner RH, Hein J, Krenz U, Schneider M. Electrical brain stimulation (tES) improves learning more than performance: A meta-analysis. *Neuroscience & Biobehavioral Reviews*. 2018;84:171-181. doi:10.1016/j.neubiorev.2017.11.001

89. Pisoni A, Mattavelli G, Papagno C, Rosanova M, Casali AG, Romero Lauro LJ. Cognitive Enhancement Induced by Anodal tDCS Drives Circuit-Specific Cortical Plasticity. *Cerebral Cortex*. 2018;28(4):1132-1140. doi:10.1093/cercor/bhx021



CHAPTER 2

Does non-invasive brain stimulation modulate emotional stress reactivity?

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ABSTRACT

Excessive emotional responses to stressful events can detrimentally affect psychological functioning and mental health. Recent studies have provided evidence that non-invasive brain stimulation (NBS) targeting the prefrontal cortex (PFC) can affect the regulation of stress-related emotional responses. However, the reliability and effect sizes have not been systematically analyzed. In the present study, we reviewed and meta-analyzed the effects of repetitive transcranial magnetic (rTMS) and direct current stimulation (tDCS) over the PFC on acute emotional stress reactivity in healthy individuals. Forty sham-controlled single-session rTMS and tDCS studies were included. Separate random-effects models were performed to estimate the mean effect sizes of emotional reactivity. Twelve rTMS studies together showed no evidence that rTMS over the PFC influenced emotional reactivity. Twenty-six anodal tDCS studies yielded a weak beneficial effect on stress-related emotional reactivity (Hedges' g = -0.16, $CI_{95\%}$ = [-0.33, 0.00]). These findings suggest that a single session of NBS is insufficient to induce reliable, clinically significant effects, but also provide preliminary evidence that specific NBS methods can affect emotional reactivity. This may motivate further research into augmenting the efficacy of NBS protocols on stress-related processes.

INTRODUCTION

Stress is an integral part of life. It fundamentally serves to protect from danger and adapt to challenges. The adaptive stress response can, however, become detrimental when it is turned on too frequently or does not properly shut off[1]. Responses to stress include feelings of distress and negative emotions. Acute stress can impair executive functions[2] and adversely affect performance and decision making, such as during surgeries[3,4], emergency service operations[5] and military operations[6,7]. Moreover, chronically elevated emotional responses to stress increase long-term daily negative affect and the risk on developing affective disorders[8–10]. Finding ways to modulate acute emotional responses to stress, also called emotional stress reactivity, is therefore relevant for daily functioning and wellbeing.

Emotional stress reactivity is associated with multiple brain regions, including the amygdala, hippocampus and frontal cortical areas. The prefrontal cortex (PFC) plays an important role in regulating acute stress responses on physiological, behavioral and affective levels[11]. Within the PFC, the ventromedial part (VMPFC) contains the major structural prefrontal-amygdala connections[12] and modulates the hypothalamic-pituitary-adrenal (HPA) axis response to stress[13]. Higher activation of the VMPFC is associated with reduced amygdala activity, diminished experience of negative emotions and better fear extinction learning[14]. The lateral parts of the PFC, the dorsolateral PFC (DLPFC) and the ventrolateral PFC (VLPFC), are associated with intentional or effortful emotion regulation by employing cognitive strategies, including (re)appraisal of emotional stimuli, response inhibition, attention regulation, and working memory[15–23]. Yet, PFC structure and PFC functions are particularly vulnerable to the effects of acute and chronic stress[2,11,24,25]. Moreover, stress and anxiety symptoms, characterized by exaggerated or context-inappropriate acute emotional response to stress, are clearly related to impaired PFC functioning[26–34]. Enhancing the regulatory function of the PFC could thus improve appropriate downregulation of stress-related emotions.

In addition to targeting PFC functioning with pharmacological (see e.g.[35,36]) and psychological treatments (see e.g.[37–40]), noninvasive brain stimulation (NBS) may provide another means to modulate stress reactivity. Two widely used NBS techniques are repetitive transcranial magnetic (rTMS) and direct current stimulation (tDCS). With rTMS, magnetic pulses are delivered to the scalp that can increase or decrease neural excitability and shape synaptic plasticity in the underlying cortical areas. An increase in neural excitability is generally induced by high-frequency rTMS (pulse frequency ≥ 5 Hz), whereas a decrease in neural excitability is generally induced by low-frequency rTMS (pulse frequency 0.1 - 1 Hz)[41–45]. Theta burst stimulation (TBS) is a specific form of rTMS using trains of three 50-Hz pulses repeated every 200 ms. When delivery of these pulse trains is intermitted by 8-second pauses, neural excitability generally increases, while neural excitability generally decreases when the pulse trains are delivered continuously or prolonged[44,46]. To control for placebo effects, active rTMS is compared to sham rTMS, where the rTMS coil is tilted or equipped with a magnetic shield to mimic the clicking sounds and, to some extent, the peripheral skin sensations without effective

brain stimulation[47]. With tDCS, a weak electrical current (1 - 2.5 mA) is applied between two electrodes placed on the scalp that can change cortical excitability in a polarity-dependent fashion[48]. Anodal tDCS generally facilitates neural excitability and plasticity, while cathodal tDCS generally decreases neural excitability and plasticity[41,42,49]. Active tDCS is commonly compared to sham tDCS, where the current is only ramped up and down at the beginning of the stimulation to mimic skin sensations without any effective stimulation of the brain[50]. When applied to the PFC, both rTMS and tDCS effects also influence brain regions that are distal but connected to the stimulated region, including contralateral prefrontal areas and limbic regions such as the amygdala[51]. To illustrate the rTMS- and tDCS-induced electric field distributions over the cortical surface, **Figure 1** depicts simulated images based on two examples of NBS montages that can be used for prefrontal NBS.

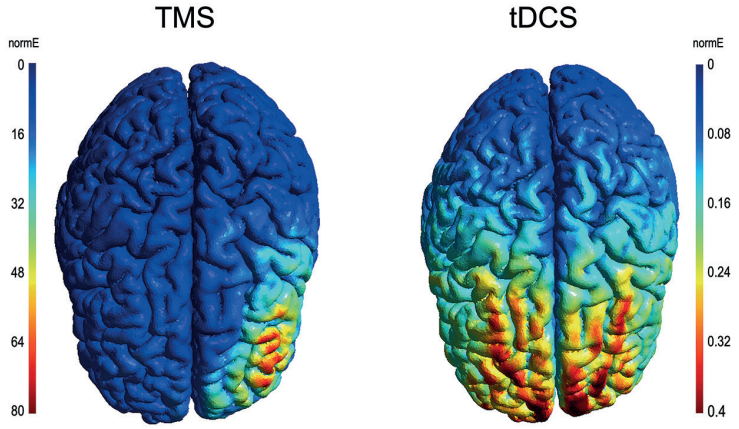

Figure 1. Example of simulated images of induced electric fields by an rTMS and a tDCS montage (SimNIBS 2.1[276]). Note the difference in focality and magnitude of the electric fields induced by the two NBS techniques. The depicted rTMS-induced field simulation is based on pulses from a figure-of-eight double 70 mm coil placed over the 10-20 system electrode position F3 (left DLPFC). The depicted tDCS-induced field simulation is based on a direct current with an intensity of 2.0 mA flowing between a 5x7 cm anode and a 5x7 cm cathode, placed over electrode position F3 (left DLPFC) and Fp2 respectively.

Some evidence for the effectivity of rTMS and tDCS in modulating stress- and emotion-related processes comes from NBS interventions that have been carried out in the area of stress-related affective disorders. For example, applying rTMS over the DLPFC can reduce symptoms of depression[52–55], PTSD[56–60], and possibly also generalized anxiety and panic disorder[61–65]. However, some studies showed no effects[66,67] and uncertainties remain regarding the optimal rTMS settings, such as pulse frequency[68] and target region[59]. Effects of tDCS on stress-related symptoms have to date been investigated to a lesser extent than rTMS. Nonetheless, there is evidence that anodal tDCS over the left DLPFC reduces depressive symptoms[69]. Moreover, two

sham-controlled studies showed significantly reduced PTSD symptoms after interventions with bilateral tDCS over the DLPFC[70] or anodal tDCS over the VMPFC during trauma exposure[71]. Further reports of tDCS effects on anxiety are summarized by Vicario and colleagues (2019)[65].

Although these effects of NBS interventions on stress-related symptoms look promising, the evidence remains inconclusive and leaves unclear how NBS is influencing stress- and emotion-related processes. Therefore, NBS effects on underlying biological and cognitive mechanisms of stress and emotion have been further examined in many experimental studies in healthy volunteers that investigate how acute stress-related processes are affected directly after NBS. Such studies showed, for example, that a single session of prefrontal NBS does not directly change baseline mood in healthy individuals[72]. On the other hand, some prefrontal NBS methods, such as high-frequency rTMS and anodal tDCS to the DLPFC, influence cognitive processes that support the regulation of acute emotional stress reactions; applying these prefrontal NBS methods in a single session already enhances working memory performance[73–75], may adjust attentional bias to threat[76,77], and can modulate identification and retrieval of emotional information, response inhibition and risky decision-making[76,78–82]. Furthermore, a recent meta-analysis showed that a single session of high-frequency rTMS and, to a lesser extent, anodal tDCS to the PFC, attenuates activity of the autonomic nervous system[83], which plays an important role in the acute physiological stress response.

Together this suggests that prefrontal NBS could modulate how one responds to stress. Several NBS studies on emotional stress reactivity have already been performed, where NBS is applied either directly before or during a stress manipulation. Laboratory stress manipulations are typically used, such as exposing participants to aversive visual material like arousing pictures or movie clips with emotionally negative content. Because aversive stimulus viewing paradigms use symbolic representations of a stressor (e.g., pictures of mutilated bodies), these paradigms can be considered passive stress inductions. Other studies use psychosocial stress manipulations, such as the Trier social stress test (TSST)[84] or social exclusion in the Cyberball game[85]. Aversive physical or auditory stimuli can also be used to induce stress, such as cold, heat or pain, or electrical shocks and loud noises in fear conditioning paradigms. All these laboratory stress manipulations increase feelings of unpleasantness and arousal and elicit immediate stress responses at the level of the sympathetic nervous system[86–97]. Stress responses at the level of the HPA-axis can also be elicited, particularly by psychosocial stressors[89,98], prolonged physical stressors[95], cognitive challenge stressors[99], and, to some extent, negative mood inductions[100–102]. Next to behavioral and physiological reactivity, the subjective experience of emotions represents another aspect of the stress response[103,104]. Emotional experiences in response to these stress manipulations are usually measured by self-report on negative emotional state scales or questionnaires, assessed during or directly after the stress manipulation. Emotional reactivity can also be assessed by rating the perceived emotional content of aversive stimuli used in the stress manipulation[88]. Such laboratory stressors and emotional measurements provide a controlled environment to assess the direct effects of NBS on subjective emotional stress reactivity.

Individual NBS studies on emotional reactivity may use diverse NBS techniques, diverse stress manipulations and diverse measurement methods. The findings across these different studies could collectively demonstrate the immediate effects of NBS on global emotional reactivity, and thereby provide insights into the usefulness of a single session of NBS in modulating affective stress responses. Therefore, we assembled all measurements of self-reported emotional responses to stress after a single session of prefrontal NBS from previous studies. This systematic review aims to provide an interim overview and quantification of the effects of rTMS and tDCS studies with healthy participants. Since effectiveness of rTMS and tDCS may diverge[83,105] and pulse frequency or current polarity may determine the direction of effects, results of low- and high-frequency rTMS and of anodal and cathodal tDCS were considered separately. Where the sample size of studies in the analyses allowed, we additionally examined the quantitative influence of targeted hemisphere (left PFC vs. right PFC) and type of stress (passive stress induction, psychosocial stress or physical or auditory stress).

METHOD

LITERATURE SEARCH

The electronic databases MEDLINE, Web of Science Core Collection and Scopus were systematically searched for rTMS and tDCS studies assessing self-reported emotional state in response to a stress induction. We retrieved articles up to October 2019.

Our search contained the following terms: *Non-invasive brain/cortical stimulation, transcranial brain stimulation, transcranial electrical/direct current stimulation, repetitive transcranial magnetic stimulation, theta burst stimulation, stress/stressor, threat, fear, anxiety/anxious, emotion/emotional, aggression/aggressive.* To concentrate on adult human studies, we added: *human, individuals, participants, subjects, men, women*, *NOT child, NOT infant*. Because we focused on the PFC, we added: *prefrontal, frontal, PFC*. The exact search terms per database are provided in the appendix.

LITERATURE REVIEW

The Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) Statement[106] and Cochrane Handbook[107] guided this quantitative review. First, two authors (FS and EG) independently reviewed titles and abstracts on suitability. Second, full text copies of the remaining articles were evaluated for inclusion and study references were screened for further relevant articles. Discrepancies in judgement of eligibility were resolved by consensus (FS, EG and DS).

ELIGIBILITY CRITERIA

Retrieved studies were selected if they fulfilled the following criteria:

a. The report is published in a peer-reviewed journal.

b. The study design includes a control condition. Eligible control conditions are restricted to the commonly used methods to apply sham stimulation as described in the Introduction.
c. The study procedure includes a stress induction. A stress induction was defined as any adverse or demanding condition that exposes participants to physical, psychosocial, mental (cognitive) or emotional stress. Emotional stress involves stimuli inducing negative stress-related emotions such as fear, anxiety or anger. Studies with sadness-inducing manipulations were also included because they elicit responses that resemble other negative emotion inductions (e.g., fear) in terms of amygdala reactivity[108], sympathetic nervous system reactivity[109], HPA-axis reactivity[100,102], and feelings of unpleasantness and arousal[110].
d. The study procedure includes the application of rTMS or tDCS over the PFC, with the aim to modulate the outcome measure.
e. The study aims to test NBS effects on emotional responses to a stress induction.
f. The study reports data of subjective negative emotional state measured within the time frame of NBS (after-)effects, in response to the stress induction. This involves all kinds of self-report measures of negative emotional reactivity, including experienced negative emotions and perceived emotional content of negative stimuli (i.e., stimulus ratings). Stimulus ratings differ from ratings of experienced emotions in terms of perspective or reference (stimulus ratings are 'world-focused' while emotional experience ratings are 'self-focused'), but both ratings share features of emotional reactivity[88,111].
g. The study participants are healthy adults (18-70 years of age).
h. The study report is written in English.

DATA EXTRACTION AND PROCESSING

To evaluate the effect of prefrontal NBS on emotional reactivity, we focused on outcomes of self-report scores of emotional state questions or questionnaires. Of studies that reported such emotional stress reactivity scores, we examined which NBS methods were applied, which prefrontal region and hemisphere was targeted, what type of stress was induced, which task or context was used in the experiment, which state or trait factors influenced the NBS effects, which NBS settings were applied (pulse/current intensity and quantity, sham condition, tDCS: location of reference electrode), and how and when the outcome was measured.

For additional quantitative analyses, mean scores of emotional reactivity and corresponding standard deviations for the active NBS and sham conditions were extracted from each paper, its supplementary materials, or from data provided by authors on request. If these data were presented in graphs, we extracted the numerical scores and corresponding standard deviations in Plot Digitizer (plotdigitizer.sourceforge.net). The emotional state scores assessed during or after NBS (final emotional state scores) were used as the outcome variable in our analyses. If final scores were not available, we used the change-from-baseline scores instead (n = 3), which theoretically addresses the same underlying effect as the final scores in randomized controlled studies[107]. Higher scores corresponded to stronger negative emotion in most studies. If a reversed scale was used in the original study (i.e. higher scores

corresponded to weaker emotion), group mean values were transformed to get in line with the other data by subtracting the original group mean values from the maximum score of the applied scale. Finally, Hedges' g effect size[112] was calculated for each separate experiment or outcome with the R package Metafor[113,114]. The correction for overestimating effect sizes in small study samples was applied[115], resulting in a corrected Hedges' g (also known as Hedges' d). Negative effect sizes following from these computations indicate that active NBS lowered negative emotional stress reactivity relative to the sham condition.

We estimated the weighted mean effect sizes in separate random-effects models for studies using high-frequency rTMS or intermittent TBS protocols, for low-frequency rTMS, prolonged intermittent TBS or continuous TBS protocols, for anodal tDCS, and for cathodal tDCS. The majority of studies reported more than one experiment or outcome of emotional reactivity. To be complete, we included all emotional reactivity outcomes from each study. We controlled for the dependence among effect sizes from the same study by applying robust variance estimation (RVE)[116,117] using the R package Robumeta[118], Metafor[114], and ClubSandwich[119]. With RVE, a covariance matrix is estimated for correlated effects. sizes were also corrected for small samples[120]. Second, we investigated if target hemisphere (left PFC vs. right PFC) and type of stress induction (passive stress induction vs. psychosocial stress vs. aversive physical or auditory stress) influenced the effect of prefrontal NBS on emotional reactivity by adding these factors as categorical moderators to the model. The target hemisphere for tDCS was defined as the hemisphere that was the intended target of the original study, or, in case of a bipolar electrode montage, the hemisphere that was targeted by the anodal electrode. Moderator analyses were only carried out if each subgroup in the analysis contained data from at least four different studies.

QUALITY AND RISK OF BIAS ASSESSMENT

Methodological quality of each study was scored based on adequate reporting, external and internal validity and possible confounders, according to the study quality assessment tool for interventions in health care[121]. Additionally, risk of bias in the method and concealment of group allocation, blinding, selective outcome reporting, and other sources of potential bias (e.g., conflicts of interest) were assessed according to the tool of Hartling and colleagues (2012)[122]. We assessed risk of publication bias by visually inspecting asymmetry in funnel plots of effect sizes against their standard errors for samples with at least ten different studies. Funnel plot asymmetry was also formally tested by an Egger's regression test.

RESULTS

The systematic literature search yielded 419 studies (**Figure 2**). We added 10 studies identified from the references of the retrieved articles. After removing duplicate research, the titles and abstracts of 424 studies were screened for eligibility. Of these, 125 potentially relevant articles were selected for full text evaluation, including 50 studies that fulfilled the eligibility criteria. This final set contained 40 (80%) studies that reported or provided on request the numerical data of emotional state measures or emotional stimulus ratings, including 118 separate outcomes.

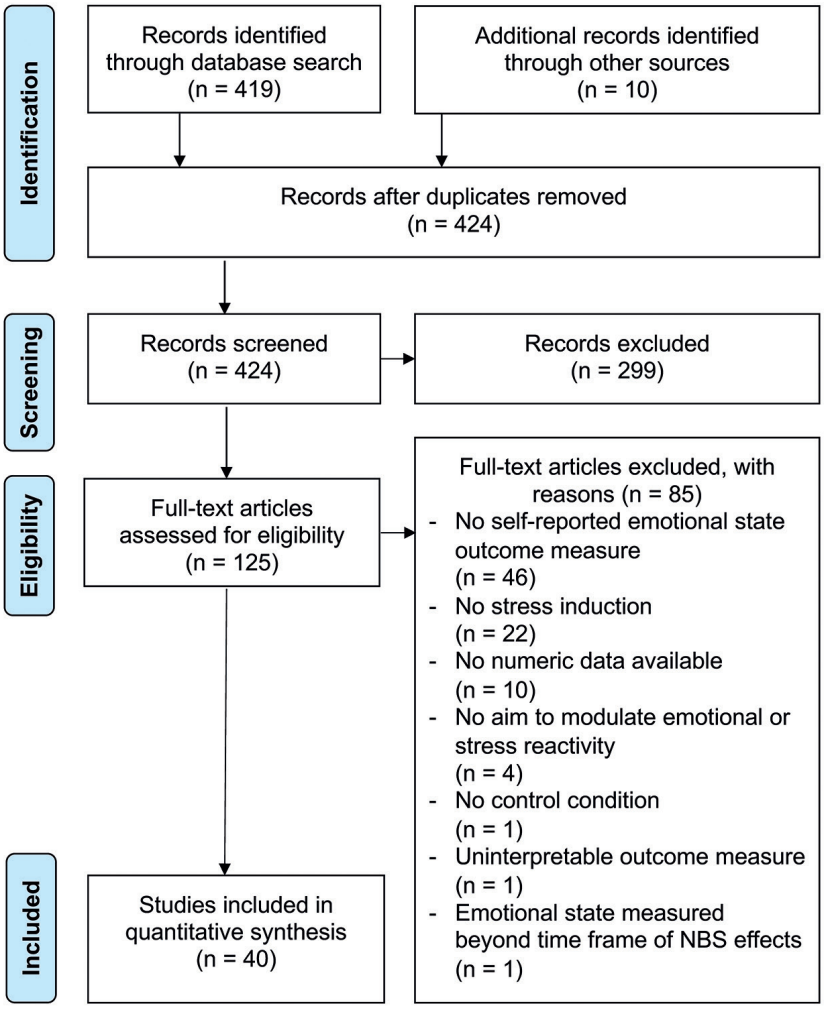

Figure 2. PRISMA flow diagram.

STUDY CHARACTERISTICS

All included studies were performed in healthy young individuals who were free from current psychiatric or neurological conditions. The majority of studies used mixed gender samples, except for seven exclusively female study samples and four exclusively male study samples. Other study details can be found in **Table 1** and **Table 2**. All stimulation-related changes in emotional stress reactivity discussed below are described in comparison to results from sham conditions.

Table 1. Characteristics of included rTMS studies

Reference	Design, Sample size n(active)|n(control)	Coil position (localization method)	Stimulation frequency, Quantity, Intensity	Control condition	Timing stress induction; Timing outcome measure	Task / Stress induction	Outcome Measure
HF-rTMS							
Studies with passive stress induction							
Möbius et al. (2017)[128]	within-subjects, 23|~	left DLPFC (F3, 10-20)	10 Hz, 3000 pulses, 110% rMT	coil tilted 45°	Stress induction: 5 min. after stimulation; Measure: immediately after stress induction	Watching sad movie clips	Sadness (Likert: 1-10), PANAS-negative affect
Berger et al. (2017) (I)[125]	within-subjects (females only), 20|~	right DLPFC (5 cm anterior to rMT region)	10 Hz, 900 pulses, 110% rMT	sham coil	Stress induction: 10 min. after stimulation; Measure: during stress induction	Watching negative IAPS pictures	Perceived picture arousal and valence (SAM: 1-9)
Jansen et al. (2019)[126]	between-subjects, 18|18	right DLPFC (neuronavigation to individual activation peak during emotion regulation)	10 Hz, 3000 pulses, 110% rMT	coil tilted 90°	Stress induction: directly after stimulation; Measure: during stress induction	Watching negative IAPS pictures	Negative emotional experience (VAS: 0-100)
Studies with psychosocial stress							
Baeken et al. (2014)[123]	within-subjects (females only), 31|~	left DLPFC (middle frontal gyrus, neuronavigation)	20 Hz, 1560 pulses, 110% rMT	coil tilted 90°	Stress induction: 5-10 min. after stimulation; Measure: immediately after stress induction	Mental counting task with bogus negative feedback	Anger and depression scales of POMS (VAS: 0-100)

Table 1. (Continued)

Reference	Design, Sample size n(active)|n(control)	Coil position (localization method)	Stimulation frequency, Quantity, Intensity	Control condition	Timing stress induction; Timing outcome measure	Task / Stress induction	Outcome Measure
Studies with aversive physical or auditory events							
Guhn et al. (2014)[129]	between-subjects, 32|30	right VMPFC (NIRS channel 26)	10 Hz, 1560 pulses, 110% rMT	sham coil	Fear acquisition before stimulation, fear extinction after stimulation; Measure: 5-10 min. after stimulation, during fear extinction.	Fear extinction learning with 95 dB aversive screams	Subjective arousal and valence* in response to fear-conditioned stimulus (SAM: 1-9)
iTBS							
Studies with passive stress induction							
Notzon et al. (2018)[127]	between-subjects, 21|20	right DLPFC (F4, 10-20)	iTBS, 600 pulses, 80% rMT	coil tilted 90°	Stress induction: 5-10 min. after stimulation; Measure: 5 min. after stress induction	Watching fearful face pictures	Perceived picture arousal and valence (SAM: 1-9)
Studies with psychosocial stress							
De Witte et al. (2020)[124]	within-subjects (females only), 38|~	left DLPFC (middle frontal gyrus, neuronavigation)	iTBS, 1620 pulses, 110% rMT	sham coil	Stress induction: before stimulation; Measure: immediately after stimulation	TSST	Anger and depression scales of POMS (VAS: 0-100)

Table 1. (Continued)

Reference	Design, Sample size n(active)|n(control)	Coil position (localization method)	Stimulation frequency, Quantity, Intensity	Control condition	Timing stress induction; Timing outcome measure	Task / Stress induction	Outcome Measure
LF-rTMS							
Studies with passive stress induction							
Zwanzger et al. (2014)[130]	between-subjects, 20|19	right DLPFC (5 cm anterior to rMT region)	1 Hz, 1800 pulses, 120% rMT	coil tilted 90°	Stress induction: 5-10 min. after stimulation; Measure: 5 min. after stress induction	Watching fearful face pictures	Perceived picture arousal and valence (SAM: 1-9)
Berger et al. (2017) (II)[125]	within-subjects (females only), 20|~	Right DLPFC (5 cm anterior to rMT region)	1 Hz, 900 pulses, 110% rMT	sham coil	Stress induction: 10 min. after stimulation; Measure: immediately after stress induction	Watching negative IAPS pictures	Perceived picture arousal and valence (SAM: 1-9)
Studies with psychosocial stress							
Fitzgibbon et al. (2017)[132]	between-subjects, 16|13	left DLPFC ("Beam F3")	1 Hz, 1200 pulses, 120% rMT	coil tilted 90°	Stress induction: immediately after stimulation; Measure: immediately after stress induction	Virtual ball-tossing game (Cyberball) with social exclusion manipulation	Aversive impact scale
Studies with aversive physical or auditory events							
Zwanzger et al. (2007)[131]	within-subjects, 11|~	right DLPFC (5 cm anterior to rMT region)	1 Hz, 1800 pulses, 120% rMT	sham coil	Stress induction: immediately after stimulation; Measure: immediately after stress induction	Panic attack induced by CCK-4 administration	Panic symptoms (API, PSS)

Table 1. (Continued)

Reference	Design, Sample size n(active)|n(control)	Coil position (localization method)	Stimulation frequency, Quantity, Intensity	Control condition	Timing stress induction; Timing outcome measure	Task / Stress induction	Outcome Measure
cTBS							
Studies with passive stress induction							
Keuper et al. (2018)[134]	between-subjects, 24|24	right DLPFC (F4, 10-20)	cTBS, 600 pulses, 80% rMT	control site stimulation (Cz)	Stress induction: immediately after stimulation; Measure: 5-10 min. after stress induction	Watching negative IAPS pictures	Perceived picture arousal and valence (VAS: 0-100)
Prolonged iTBS							
Studies with passive stress induction							
Hurlemann et al. (2015) (I)[133]	between-subjects (males only), 20|20⁺	left DLPFC (middle frontal gyrus, neuronavigation)	iTBS, 1200 pulses, 80% rMT	sham coil	Stress induction: immediately after stimulation; Measure: immediately after stress induction	Watching negative IAPS pictures	Perceived picture arousal and valence (SAM: 1-9)
Hurlemann et al. (2015) (II)[133]	between-subjects (males only), 20|20⁺	left DMPFC (superior frontal gyrus, neuronavigation)	iTBS, 1200 pulses, 80% rMT	sham coil	Stress induction: immediately after stimulation; Measure: immediately after stress induction	Watching negative IAPS pictures	Perceived picture arousal and valence (SAM: 1-9)

⁺ indicates samples used for multiple experiments within a study; * indicates measures that are not included in the meta-analysis due to insufficient available numerical data; 10-20 = 10-20 system for localizing scalp electrodes; API = Acute Panic Inventory[277]; "Beam F3" = freeware to determine location of DLPFC[278]; Cyberball = Cyberball game[85]; cTBS = continuous theta burst stimulation; iTBS = intermittent theta burst stimulation; IAPS = International Affective Picture System[88]; Likert = Likert scale; MDMQ = Multidimensional Mood State Questionnaire[279]; PANAS = Positive and Negative Affect Schedule[280]; PMFC = posterior medial frontal cortex; POMS = Profile of Mood States[281]; PSS = Panic Symptom Scale[282]; rMT = resting motor threshold; SAM = Self-assessment Manikin.

Table 2. Characteristics of included tDCS studies

Reference	Design, Sample size n(active)| n(control)	Electrode positions (localization method)	Current intensity, Anode + cathode size, Quantity	Control condition	Timing stress induction; Timing outcome measure	Task / Stress induction	Outcome Measure
A-tDCS							
Studies with passive stress induction							
Boggio et al. (2009)[141]	Within-subjects, 23|~	Left DLPFC (anode: F3, cathode: Fp2, 10-20)	2 mA, 35 + 35 cm^2, 5 min.	Current ramped down after 30 s	Stress induction: during stimulation; Measure: during stimulation	Watching pictures of human pain	Perceived picture valence and emotional discomfort (Likert: 1-9)
Peña-Gómez et al. (2011) (I)[142]	Within-subjects (females only), 16|~	Left DLPFC (anode: F3, cathode: C4, 10-20)	1 mA, 35 + 35 cm^2, 20 min.	Current ramped down after 30 s	Stress induction: during stimulation; Measure: during stimulation	Watching negative IAPS pictures	Perceived picture valence (Likert: 1-9)
Maeoka et al. (2012)[143]	Within-subjects, 15|~	Left DLPFC (anode: F3, cathode: Fp2, 10-20)	1 mA, 35 + 35 cm^2, 20 min.	Current ramped down after 30 s	Stress induction: immediately after stimulation; Measure: immediately after stress induction	Watching negative IAPS pictures	Perceived picture arousal* and valence (SAM: 1-9)
Brunoni et al. (2013) (I)[75]	Within-subjects, 20|~+	Left DLPFC (anode: F3, cathode: F4, 10-20)	1.5 mA, 35 + 35 cm^2, 33 min.	Current ramped down after 30 s	Stress induction: during stimulation; Measure: during stimulation	Watching negative IAPS pictures	Negative mood and state anxiety (VAS: 0-100)
Brunoni et al. (2013) (II)[75]	Within-subjects, 20|~+	Right DLPFC (anode: F4, cathode: F3, 10-20)	1.5 mA, 35 + 35 cm^2, 33 min.	Current ramped down after 30 s	Stress induction: during stimulation; Measure: during stimulation	Watching negative IAPS pictures	Negative mood and state anxiety (VAS: 0-100)
Feeser et al. (2014)[154]	Between-subjects, 21|21	Right DLPFC (anode: F4, cathode: Fp1, 10-20)	1.5 mA, 35 + 100 cm^2, 20 min.	Current ramped down after 30 s	Stress induction: during stimulation; Measure: during stimulation	Watching negative IAPS pictures, with and without downregulation instructions	Subjective arousal in response to pictures (Likert: 1-9), depressed mood (MDMQ)

Table 2. (Continued)

Reference	Design, Sample size n(active)| n(control)	Electrode positions (localization method)	Current intensity, Anode + cathode size, Quantity	Control condition	Timing stress induction; Timing outcome measure	Task / Stress induction	Outcome Measure
Rêgo et al. (2015) (I)[144]	Between-subjects, 8|8•	Left DLPFC (anode: F3, cathode: F4, 10-20)	2 mA, 35 + 35 cm^2, 15 min.	Current ramped down after 30 s	Stress induction: during stimulation; Measure: during and immediately after stimulation	Watching videos of human pain	Subjective arousal and valence in response to videos (SAM: 1-9), Mood scales: alert*, confused*, attentive*, sad; hostile (VAS: 0-9)
Rêgo et al. (2015) (II)[144]	Between-subjects, 8|8•	Right DLPFC (anode: F4, cathode: F3, 10-20)	2 mA, 35 + 35 cm^2, 15 min.	Current ramped down after 30 s	Stress induction: during stimulation; Measure: during and immediately after stimulation	Watching videos of human pain	Subjective arousal and valence in response to videos (SAM: 1-9), Mood scales: alert*, confused*, attentive*, sad; hostile (VAS: 0-9)
Vierheilig et al. (2016) (I)[137]	Between-subjects, 18|18•	Left DLPFC (anode: F3, cathode: F4, 10-20)	1 mA, 35 + 35 cm^2, 20 min.	Current ramped down after 20 s	Stress induction: during stimulation; Measure: immediately after stress induction	Watching negative IAPS mutilation pictures	Perceived picture valence* and arousal (SAM: 1-9), PANAS-negative affect
Vierheilig et al. (2016) (II)[137]	Between-subjects, 16|18•	Right DLPFC (anode: F4, cathode: F3, 10-20)	1 mA, 35 + 35 cm^2, 20 min.	Current ramped down after 20 s	Stress induction: during stimulation; Measure: immediately after stress induction	Watching negative IAPS mutilation pictures	Perceived picture valence* and arousal (SAM: 1-9), PANAS-negative affect

Table 2. (Continued)

Reference	Design, Sample size n(active)| n(control)	Electrode positions (localization method)	Current intensity, Anode + cathode size, Quantity	Control condition	Timing stress induction; Timing outcome measure	Task / Stress induction	Outcome Measure
Chen et al. (2017)[156]	Between-subjects, 23|25	Left DLPFC (anode: F3, 10-20, cathode: left neck)	2 mA, 24 + 24 cm^2, 20 min	Current ramped down after 60 s	Stress induction: immediately after stimulation; Measure: immediately after stress induction	Watching real-life threat and neutral videos	STAI-6
Voss et al. (2018) (I)[135]	Between-subjects (females only), 40|40•	Left DLPFC (anode: F3, 10-20, cathode: right shoulder)	1 mA, 35 + 35 cm^2, 20 min.	Current ramped down after 30 s	Stress induction: immediately after stimulation; Measure: 10 min. after stress induction	Watching sexual and physical abuse video	Subjective arousal and negative mood in response to videos (SAM: 1-9)
Marques et al. (2018) (I)[155]	Between-subjects, 30|30•	Left DLPFC (anode: F3, cathode: F4, 10-20)	1.5 mA, 16 + 16 cm^2, 20 min.	Current ramped down after 30 s	Stress induction: during stimulation; Measure: during stimulation	Watching negative IAPS pictures, with and without downregulation instructions	Subjective valence and arousal in response to pictures (SAM: 1-9), PANAS-negative affect*
Marques et al. (2018) (II)[155]	Between-subjects, 30|30•	Right DLPFC (anode: F4, cathode: F3, 10-20)	1.5 mA, 16 + 16 cm^2, 20 min.	Current ramped down after 30 s	Stress induction: during stimulation; Measure: during stimulation	Watching negative IAPS pictures, with and without downregulation instructions	Subjective valence and arousal in response to pictures (SAM: 1-9), PANAS-negative affect*
He et al. (2018) (I)[153]	Between-subjects, 23|21	Right VLPFC (anode: F6, cathode: Fp1, 10-20)	2.5 mA, 25 + 25 cm^2, 24 min.	Current ramped down after 30 s	Stress induction: during stimulation; Measure: during stimulation	Watching pictures of social exclusion, with and without downregulation instructions	Perceived negative emotion in picture (Likert: 1-9)

Table 2. (Continued)

Reference	Design, Sample size n(active)| n(control)	Electrode positions (localization method)	Current intensity, Anode + cathode size, Quantity	Control condition	Timing stress induction; Timing outcome measure	Task / Stress induction	Outcome Measure
He et al. (2018) (II)[153]	Between-subjects, 20|20	Right VLPFC (anode: F6, cathode: Fp1, 10-20)	2.5 mA, 25 + 25 cm^2, 24 min.	Current ramped down after 30 s	Stress induction: during stimulation; Measure: during stimulation	Watching pictures of social exclusion, with and without downregulation instructions	Perceived negative emotion in picture (Likert: 1-9)
Marques et al. (2018) (III)[155]	Between-subjects, 29|30••	Left VLPFC (anode: F7, cathode: F8, 10-20)	1.5 mA, 16 + 16 cm^2, 20 min.	Current ramped down after 30 s	Stress induction: during stimulation; Measure: during stimulation	Watching negative IAPS pictures, with and without downregulation instructions	Subjective valence and arousal in response to pictures (SAM: 1-9), PANAS-negative affect*
Marques et al. (2018) (IV)[155]	Between-subjects, 30|30••	Right VLPFC (anode: F8, cathode: F7, 10-20)	1.5 mA, 16 + 16 cm^2, 20 min.	Current ramped down after 30 s	Stress induction: during stimulation; Measure: during stimulation	Watching negative IAPS pictures, with and without downregulation instructions	Subjective valence and arousal in response to pictures (SAM: 1-9), PANAS-negative affect*
Vergallito et al. (2018)[149]	Between-subjects, 49|47	Right VLPFC (anode: F6, cathode: Fp1, 10-20)	1.5 mA, 25 + 35 cm^2, 20 min.	Current ramped down after 30 s	Stress induction: during stimulation; Measure: during stimulation	Watching negative emotion inducing videos	Five negative emotion DES (Likert: 1-10)
Koenigs et al. (2009) (I)[150]	Within-subjects, 21|~+	Bilateral VMPFC (anodes: Fp1 + Fp2, 10-20, cathode: non-dominant arm)	2.5 mA, 25 + 25 25 cm^2, 35 min.	Current ramped down after 30 s	Stress induction: during stimulation; Measure: during stimulation	Watching negative and positive IAPS pictures	Subjective arousal in response to pictures (Likert: 1-7), anger and depression scales of POMS (Likert: 1-5) (change score relative to baseline)

Table 2. (Continued)

Reference	Design, Sample size n(active)| n(control)	Electrode positions (localization method)	Current intensity, Anode + cathode size, Quantity	Control condition	Timing stress induction; Timing outcome measure	Task / Stress induction	Outcome Measure
Abend et al. (2018)[152]	Within-subjects, 16|~	VMPFC (anode: above nasion, cathode: beneath inion)	1.5 mA, 35 + 35 cm^2, 20 min.	Current ramped down after 30 s	Stress induction: during stimulation; Measure: during and after stimulation	Watching frightening or violent videos	Subjective emotion intensity (Likert: 1-4), anxiety (VAS: 0-30)
Studies with psychosocial stress							
Hortensius et al. (2012) (I)[159]	Between-subjects, 21|19•	Left DLPFC (anode: F3, cathode: F4, 10-20)	2 mA, 35 + 35 cm^2, 15 min.	Current ramped down after 40 s	Stress induction: before stimulation; Measure: 5-10 min. after stimulation (change score relative to baseline)	Essay writing with negative social feedback	Anger (Likert: 1-5)
Hortensius et al. (2012) (II)[159]	Between-subjects, 20|19•	Right DLPFC (anode: F4, cathode: F3, 10-20)	2 mA, 35 + 35 cm^2, 15 min.	Current ramped down after 40 s	Stress induction: before stimulation; Measure: 5-10 min. after stimulation (change score relative to baseline)	Essay writing with negative social feedback	Anger (Likert: 1-5)
Riva et al. (2012)[148]	Between-subjects, 19|19	Right VLPFC (anode: F8, cathode: Fp1, 10-20)	1.5 mA, 25 + 35 cm^2, 15 min.	Current ramped down after 15 s	Stress induction: during stimulation; Measure: immediately after stress induction	Virtual ball-tossing game (Cyberball) with social exclusion manipulation	Unpleasantness (Likert: 1-10)
Kelley et al. (2015) (I)[160]	Between-subjects, 14|16•	Left DLPFC (anode: F3, cathode: F4, 10-20)	2 mA, 35 + 35 cm^2, 15 min.	Current ramped down after 30 s	Stress induction: during stimulation; Measure: immediately after stress induction	Virtual ball-tossing game (Cyberball) with social exclusion manipulation	Jealousy (Likert: 1-9)

Table 2. (Continued)

Reference	Design, Sample size n(active)| n(control)	Electrode positions (localization method)	Current intensity, Anode + cathode size, Quantity	Control condition	Timing stress induction; Timing outcome measure	Task / Stress induction	Outcome Measure
Kelley et al. (2015) (II)[160]	Between-subjects, 15|16•	Right DLPFC (anode: F4, cathode: F3, 10-20)	2 mA, 35 + 35 cm^2, 15 min.	Current ramped down after 30 s	Stress induction: during stimulation; Measure: immediately after stress induction	Virtual ball-tossing game (Cyberball) with social exclusion manipulation	Jealousy (Likert: 1-9)
Plewnia et al. (2015)[146]	Between-subjects (males only), 14|14	Left DLPFC (anode: F3, 10-20, cathode: right shoulder)	1 mA, 35 + 35 cm^2, 20 min.	Current ramped down after 30 s	Stress induction: 5 min. after stimulation + 20 min. after stimulation; Measure: immediately after 2nd stress induction	Frustrating mental counting task (PASAT)	PANAS-negative affect
Bogdanov and Schwabe (2016) (I)[139]	Between-subjects, 20|20•	Right DLPFC (anode: F4, cathode: Cz, 10-20)	1.075 mA, 25 + 100 cm^2, 6-10 min.	Current ramped down after 13 s	Stress induction: 20 min. before stimulation; Measure: immediately after stimulation	TSST	Depressed mood (MDMQ)
Baeken et al. (2018)[138]	Within-subjects (females only), 28|~	Left DLPFC (anode: (middle frontal gyrus, neuronavigation, cathode: Fp2, 10-20)	1.5 mA, 25 + 25 cm^2, 20 min.	Current ramped down after 30 s	Stress induction: 5 min. after stimulation; Measure: immediately after stress induction	Hearing verbal criticism	Anger and depression scales of POMS (VAS: 0-100)
Carnevali et al. (2019)[145]	Between-subjects (males only), 15|15	Left DLPFC (anode: F3, 10-20, cathode: F4)	2 mA, 35 + 35 cm^2, 15 min.	Current ramped down after 30 s	Stress induction: during stimulation; Measure: 30 min. after stress induction	Stressful interview and arithmetic task	STAI-state

Table 2. (Continued)

Reference	Design, Sample size n(active)| n(control)	Electrode positions (localization method)	Current intensity, Anode + cathode size, Quantity	Control condition	Timing stress induction; Timing outcome measure	Task / Stress induction	Outcome Measure
Antal et al. (2014) (I)[151]	Between-subjects (males only), 20|20•	Right VMPFC (anode: between F2-Fpz, cathode: between O2-P4, 10-20)	1 mA, 35 + 35 cm^2, 20 min.	Current ramped down after 30 s	Stress induction: immediately after stimulation; Measure: immediately after stress induction	TSST	STAI-state (change score relative to baseline)
Studies with aversive physical or auditory events							
Deldar et al. (2018)[136]	Within-subjects, 20|~	Left DLPFC (anode: F3, 10-20 cathode: right shoulder)	2 mA, 35 + 35 cm^2, 22 min.	Current ramped down after 46 s	Stress induction: during stimulation; Measure: during stimulation	Pain by electrical stimulation with and without concurrent cognitive (working memory) task	State anxiety (NRS: 0-100)
Herrmann et al. (2018)[147]	Between-subjects, 31|49	Right VLPFC (anode: 1.5 cm posterior to F6, cathode: 1.5 cm from Fp1 towards Fpz, 10-20)	2 mA, 35 + 35 cm^2, 20 min.,	Current ramped down after 20 s	Stress induction: during stimulation; Measure: immediately after stress induction	Sustained threat paradigm with 98 dB aversive screams	Subjective valence, arousal and anxiety in response to threat-associated stimulus (Likert: 1-9), STAI-state, PANAS-negative affect
Abend et al. (2016)[158]	Between-subjects, 15|14	VMPFC (anode: above nasion, cathode: beneath inion)	1.5 mA, 35 + 35 cm^2, 20 min.	Current ramped down after 30 s	Fear acquisition before stimulation, fear extinction during stimulation; Measure: immediately after extinction	Fear extinction learning after conditioning with 80 dB aversive screams	Conditioned stimulus fear (Likert: 1-10)

Table 2. (Continued)

Reference	Design, Sample size n(active)| n(control)	Electrode positions (localization method)	Current intensity, Anode + cathode size, Quantity	Control condition	Timing stress induction; Timing outcome measure	Task / Stress induction	Outcome Measure
Dittert et al. (2018) (I)[157]	Between-subjects, 40|27	Right VMPFC (anode: beneath F8, cathode: beneath F7, 10-20)	1.5 mA, 16 + 16 cm^2, 20 min.	Current ramped down after 60 s	Fear acquisition before stimulation, fear extinction during stimulation; Measure: during stimulation, during extinction	Fear extinction learning after conditioning with 95 dB aversive screams	STAI-state, PANAS-negative affect, subjective valence* and arousal* in response to fear-conditioned stimulus (Likert: 1-9)
Dittert et al. (2018) (II)[157]	Between-subjects, 37|26	Left VMPFC (anode: beneath F7, cathode: beneath F8, 10-20)	1.5 mA, 16 + 16 cm^2, 20 min.	Current ramped down after 60 s	Fear acquisition before stimulation, fear extinction during stimulation; Measure: during stimulation, during extinction	Fear extinction learning after conditioning with 95 dB aversive screams	STAI-state, PANAS-negative affect, subjective valence* and arousal* in response to fear-conditioned stimulus (Likert: 1-9)
C-tDCS							
Studies with passive stress induction							
Peña-Gómez et al. (2011) (II)[142]	Within-subjects (females only), 9|~	Left DLPFC (cathode: F3, anode: C4, 10-20)	1 mA, 35 + 35 cm^2, 20 min.	Current ramped down after 30 s	Stress induction: during stimulation; Measure: during stimulation	Watching negative IAPS pictures	Perceived picture valence (Likert: 1-9)
Voss et al. (2018) (II)[135]	Between-subjects (females only), 38|40•	Left DLPFC (cathode: F3, 10-20, anode: right shoulder)	1 mA, 35 + 35 cm^2, 20 min.	Current ramped down after 30 s	Stress induction: immediately after stimulation; Measure: 10 min. after stress induction	Watching sexual and physical abuse video	Subjective arousal and negative mood in response to videos (SAM: 1-9)

Table 2. (Continued)

Reference	Design, Sample size n(active)| n(control)	Electrode positions (localization method)	Current intensity, Anode + cathode size, Quantity	Control condition	Timing stress induction; Timing outcome measure	Task / Stress induction	Outcome Measure
Koenigs et al. (2009) (II)[150]	Within-subjects, 21|~+	Bilateral VMPFC (cathodes: Fp1 + Fp2, 10-20, anode: non-dominant arm)	2.5 mA, 25 + 25 + 25 cm^2, 35 min.	Current ramped down after 30 s	Stress induction: during stimulation; Measure: during stimulation (change score relative to baseline)	Watching negative and positive IAPS pictures	Subjective arousal in response to pictures (Likert: 1-7), anger and depression scales of POMS (Likert: 1-5) (change score relative to baseline)
Studies with psychosocial stress							
Riva et al. (2015)[162]	Between-subjects, 20|20	Right VLPFC (cathode: F6, anode: Fp1, 10-20)	1.5 mA, 25 + 35 cm^2, 20 min.	Current ramped down after 15 s	Stress induction: during stimulation; Measure: immediately after stress induction	Virtual ball-tossing game (Cyberball) with social exclusion manipulation	Negative emotions (Likert: 1-10)
Bogdanov and Schwabe (2016) (II)[139]	Between-subjects, 20|20•	Right DLPFC (cathode: F4, anode: Cz, 10-20)	1.075 mA, 25 + 100 cm^2, 6-10 min.	Current ramped down after 13 s	Stress induction: 20 min. before stimulation; Measure: immediately after stimulation	TSST	Depressed mood (MDMQ)
Antal et al. (2014) (II)[151]	Between-subjects (males only), 20|20•	Right VMPFC (cathode: between F2-Fpz, anode: between O2-P4, 10-20)	1 mA, 35 + 35 cm^2, 20 min.	Current ramped down after 30 s	Stress induction: immediately after stimulation; Measure: immediately after stress induction (change score relative to baseline)	TSST	STAI-state

Table 2. (Continued)

Reference	Design, Sample size n(active)| n(control)	Electrode positions (localization method)	Current intensity, Anode + cathode size, Quantity	Control condition	Timing stress induction; Timing outcome measure	Task / Stress induction	Outcome Measure
Studies with aversive physical or auditory events							
Ganho-Avila et al. (2019)[161]	Between-subjects (females only), 27|16	Right DLPFC (cathode: F4, anode: left shoulder, 10-20)	1 mA, 24,75 + 24,75 cm^2, 20 min.	Current ramped down after 30 s	Stress induction: fear acquisition 24-hours before stimulation, fear reinstatement immediately before stimulation; Measure: immediately after stimulation, before and after fear extinction learning.	Fear conditioning and extinction learning with 95 dB aversive screams	Subjective valence and arousal in response to fear-conditioned stimulus (Likert: 1-9)

[+] indicates samples used for multiple experiments within a study; • and •• indicate active stimulation conditions that are compared to the same placebo group; * indicates measures that are not included in the meta-analysis due to insufficient available numerical data; 10-20 = 10-20 system for localizing scalp electrodes; A-tDCS = anodal tDCS: tDCS with the anode placed over the target brain region; C-tDCS = cathodal tDCS: tDCS with the cathode placed over the target brain region; Cyberball = a virtual ball-toss game used to study social exclusion[85]; DES = Differential Emotional Scale[283]; HD-tDCS = high-definition tDCS; IAPS = International Affective Picture System[88]; Likert = Likert scale; MDMQ = Multidimensional Mood State Questionnaire[279]; NRS = Numerical Rating Scale; PANAS = Positive and Negative Affect Schedule[280]; PASAT = Paced Auditory Serial Addition Task[284]; POMS = Profile of Mood States[281]; SAM = Self-assessment Manikin; STAI = State and Trait Anxiety Inventory[285], STAI-6 is the 6-item short form of the STAI-State; TSST = Trier Social Stress Test[286]; VAS = visual analogue scale.

RTMS

High-frequency rTMS and intermittent TBS

We identified five high-frequency rTMS studies and two intermittent TBS studies that reported in total twelve different outcomes on emotional stress reactivity. The majority of these studies focused on the DLPFC. Two studies found no effect of 20-Hz rTMS or intermittent TBS over the left DLPFC on emotional responses to psychosocial stress[123,124], and two other studies found no effect of 10-Hz rTMS over the right DLPFC on ratings of perceived emotional content or experienced negative emotion in response to aversive pictures[125,126]. Two studies did find a significant effect of NBS over the DLPFC on emotional stress reactivity. Notzon and colleagues (2018)[127], who targeted the right DLPFC, found a decrease in perceived negative valence and arousal of fearful face pictures after intermittent TBS. Möbius and colleagues (2017)[128], who instead targeted the left DLPFC, found an *increase* in experienced sadness after watching sad movie clips following 10-Hz rTMS. Please note that, different from the other stress manipulations, this stress manipulation is limited to inducing sadness. The VMPFC was targeted in one study with 10-Hz rTMS[129] which effectively reduced emotional responses to fear-conditioned stimuli during extinction learning. For further details on stimulation parameters, type of stress and experimental context of each study, see **Table 1**.

The data from this sample of studies (k = 7, n = 251) showed moderate heterogeneity (I^2 = 49.0%), and the summary analysis estimated a weighted mean effect of g = -0.06, $CI_{95\%}$ = [-0.35, 0.24], p = 0.70. Based on these few studies, this analysis showed no significant main effect and the low statistical power prevented further analysis of potential moderators.

Low-frequency rTMS, prolonged intermittent TBS and continuous TBS

We identified four low-frequency rTMS studies, one continuous TBS study, and one prolonged intermittent TBS study that reported in total fourteen different outcomes on emotional stress reactivity. All these studies focused on the DLPFC (see **Table 1** for further study details). Three of the low-frequency rTMS studies targeting the right or left DLPFC found no effect on perceived emotional content of negative pictures or on biologically induced panic[125,130,131]. The fourth low-frequency rTMS study[132] also showed no group-level differences, but did find a link between a higher aversive impact of social exclusion in the Cyberball game and higher trait personal distress after active 1-Hz rTMS to the left DLPFC, but not after sham rTMS. The authors interpret this finding in terms of brain-state dependency of rTMS effects; rTMS may have amplified emotional reactivity only in those who are more sensitive to interpersonal stress.

Of the two studies using continuous or prolonged intermittent TBS, Hurlemann and colleagues (2015)[133] found no effects of left DLPFC or left DMPFC stimulation on perceived emotional content of negative stimuli, while Keuper and colleagues (2018)[134] showed that participants perceived negative pictures as less negative and less arousing after continuous TBS to the right DLPFC.

Together, the data from these studies (k = 6, n = 207) showed low heterogeneity (I^2 = 14.3%). The summary analysis estimated a weighted mean effect of g = -0.13, ($CI_{95\%}$ = [-0.42, 0.16], p = 0.39). Also here, the low number of studies in this sample did not allow further moderator analyses.

TDCS

Anodal tDCS

We identified 26 anodal tDCS studies that reported in total 79 different outcomes on emotional stress reactivity (see **Table 2** for study details). Of the studies focusing on the DLPFC, six studies targeting the left DLPFC[75,135–138] or right DLPFC[75,137,139] found no tDCS effects on emotional stress reactivity. This number includes the study of Baeken and colleagues (2018)[138] who additionally reported no relationship between a measure of psychosocial stress sensitivity and psychosocial stress reactivity on the level of emotional experience[140]. In contrast, six other studies targeting the left DLPFC[141–145] or right DLPFC[144] did find a significant decline in emotional stress reactivity after tDCS, or at least in a subset of emotional outcomes[146]. Hence, in half of the studies targeting the DLPFC, anodal tDCS lowered emotional stress reactivity, while the other half of the studies showed no significant effects on similar outcomes. Focusing on the VLPFC, one study found no effect of anodal tDCS to the right VLPFC on emotional responses to threat of shock[147], while two studies of anodal tDCS to the same region found significantly weaker negative emotional experience in response to psychosocial stress or aversive pictures[148,149]. The VMPFC was targeted in three studies, of which two showed no tDCS effects on experienced emotions after psychosocial stress or watching aversive pictures[150,151]. The third study did find support for tDCS being able to significantly reduce emotional experience in response to aversive pictures[152]. Furthermore, a number of studies found interesting indirect anodal tDCS effects on emotional reactivity. Three studies showed that anodal tDCS only reduced emotional reactivity when participants actively downregulated their emotions, but not when participants maintained their natural emotional responses[153–155]. The first two studies showed these effects after placing the anode over the right DLFPC or right VLPFC[153,154], but the third study[155] only found significant effects after anodal stimulation of the left VLPFC with the cathode placed on the contralateral VLPFC, but not with the reversed montage or when the bilateral montage was placed over the DLPFC. In addition, Chen and colleagues (2017)[156] showed that anodal tDCS to the left DLPFC reduced attention bias towards threat videos, which was, in turn, associated with less emotional reactivity to these videos.

With regard to location of the reference electrode, the above-described studies did not show a clear influence of cathode location on the effect of anodal stimulation (see **Table 2** for cathode locations per study). Yet, a number of studies do show different effects of tDCS with different montages. For example, Dittert and colleagues (2018)[157] found that bilateral VMPFC stimulation with the anode over the left VMPFC, but not the reversed montage, enhanced fear extinction learning, i.e. reduced fear for the conditioned stimulus when the unconditioned threat stimulus (aversive loud scream) was no longer presented. In contrast, Abend and colleagues (2016)[158], who stimulated the VMPFC by placing the anode over the forehead and the cathode on the

back of the head, found that tDCS *inhibited* fear extinction learning. Hortensius, Schutter and Harmon-Jones (2012)[159], who found no group-level differences in anger after negative social feedback, showed that a correlation between increased anger and more aggressive behavioral responses only appeared after bilateral DLPFC stimulation with the anode over the left DLPFC, but not after stimulation with the reversed montage. Similarly, Kelley and colleagues (2015)[160] found that bilateral DLPFC stimulation with the anode over the left DLPFC, but not with the anode over the right DLPFC, increased jealousy after social exclusion in the Cyberball game.

Together, the data from these studies (k = 26, n = 1284) showed moderate heterogeneity (I^2 = 48.59%). The full random-effects model showed a statistically significant weighted mean effect size of g = -0.16, $CI_{95\%}$ = [-0.33, 0.00], p = 0.05 (see **Figure 3**), indicating that anodal tDCS lowers emotional stress reactivity compared to sham tDCS. This effect was not significantly moderated by type of stress (Q(3) = 5.56, p = 0.14). The moderation of the effect by target hemisphere approached significance (Q(2) = 4.95, p = 0.08). Follow-up analyses showed a very small numerical difference between left- and right-sided effect sizes. Separate effects of left- and right-sided prefrontal tDCS were not statistically significant (right PFC: g = -0.23, $CI_{95\%}$ = [-0.48, 0.03], p = 0.08); left PFC: g = -0.17, $CI_{95\%}$ = [-0.41, 0.07], p = 0.16). The funnel plot of all A-tDCS effects together did not show significant asymmetry (see **Figure 4**, Egger's regression test: t(77) = -0.02, p = 0.99).

Cathodal tDCS

We identified seven cathodal tDCS studies that reported in total thirteen different outcomes on emotional stress reactivity. Six of these studies found no effect on emotional reactivity to negative pictures or videos or to psychosocial stress after cathodal tDCS applied over the left or right DLPFC, the right VLPFC or the VMPFC (see **Table 2** for other experimental settings)[135,139,142,150,151,161]. Only Riva and colleagues (2015)[162], who applied cathodal tDCS over the right VLPFC and placed the anode over the contralateral orbitofrontal area, showed a significant amplification of emotional reactivity to social exclusion in a Cyberball game, which was not found when the cathode was placed over the parietal cortex.

Together, the data from these studies (k = 7, n = 271) showed moderate heterogeneity (I^2 = 43.9%), and the summary analysis estimated a mean effect of g = -0.02, $CI_{95\%}$ = [-0.22, 0.28], p = 0.90. As with the rTMS analyses, the low number of studies in this sample did not allow further quantitative analyses.

QUALITY AND RISK OF BIAS

Figure 5 presents a graphical overview of methodological quality and risk of bias in the included studies. A common methodological weakness was incomplete reporting of experimental methods or results. Risk of bias in the included studies was strongest with regard to blinding: whether study personnel were blind to stimulation condition was often unclear, especially in rTMS studies where blinding procedures are more challenging than for tDCS. Additionally, although participants were typically randomized to conditions, many studies did not specify how the randomization sequence was generated, how groups were matched,

and if group allocation was concealed for study personnel, leaving it unclear if these studies dealt adequately with group-related confounders.

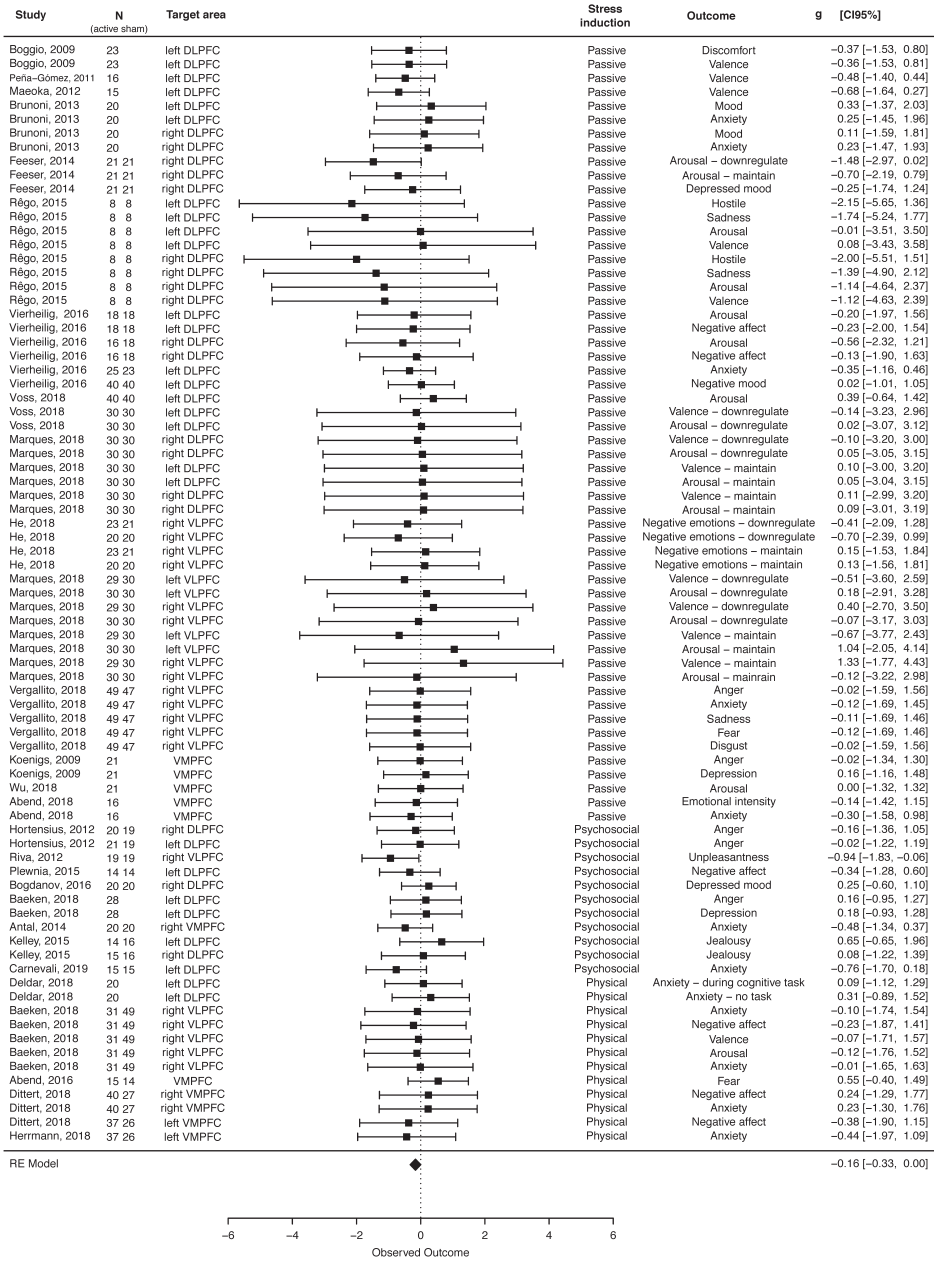

Figure 3. Forest plot of the separate outcomes of anodal tDCS studies. The figure additionally depicts for each study the sample sizes of active tDCS and sham tDCS conditions (sham sample size is left blank for cross-over studies), the target area for anodal stimulation, the type of stress induction in the experiment, and the outcome measure.

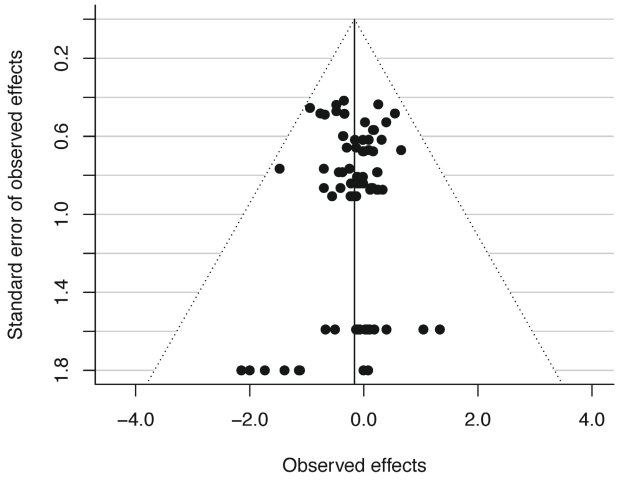

Figure 4. Funnel plot of anodal tDCS studies. Note: because two studies reported many separate outcomes[144,155], the standard errors of their effects were increased by the RVE correction. These effects therefore appear at the bottom of the plot.

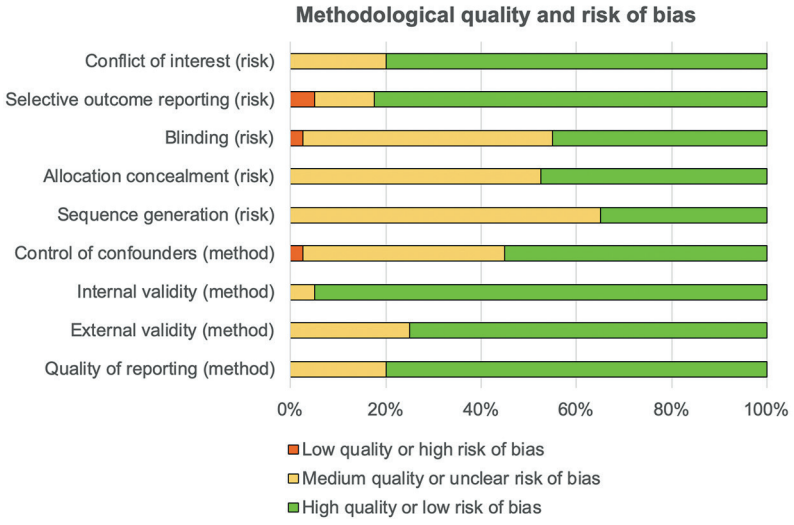

Figure 5. Methodological quality and risk of bias of the included studies.

DISCUSSION

Ongoing research efforts are dedicated to establish and understand NBS effects on stress-related processes. Experimental evidence is often derived from direct effects of single NBS sessions on acute stress. However, it has not been systematically analyzed if and how single sessions of prefrontal NBS affect stress reactivity on the level of subjective emotion in a normal-functioning stress system. We therefore systematically reviewed and quantified the immediate effects of prefrontal NBS on emotional stress reactivity in forty sham-controlled healthy participant single-session NBS studies, including 12 rTMS studies and 28 tDCS studies.

The data from these studies show that the effects of a single session of prefrontal NBS may not be strong and stable enough to induce clinically relevant effects on emotional stress reactivity in all healthy individuals. On the other hand, some methods show promising effects that are worth further investigation. Acute effects of rTMS on emotional reactivity were investigated by relatively few studies, which showed effects in different directions. Acute effects of tDCS were more widely investigated and quantitative results showed that applying anodal tDCS over the PFC overall slightly reduced negative stress-related emotions. However, effectivity of anodal tDCS varied between studies. Follow-up analyses suggested that the overall effect of anodal tDCS did not significantly depend on targeted hemisphere (left or right PFC), or on the type of stress that was induced (passive stress induction, psychosocial stress or aversive physical or auditory events). Several findings do suggest dependence of NBS effectivity on a number of other experimental and personal factors, including the NBS settings and the participant's psychological state.

Remue and colleagues (2016)[72] concluded that a single session of prefrontal NBS does not affect mood. The present results, however, give an indication that a single session of prefrontal NBS may be able to modulate negative emotional state in response to stress, at least when using anodal tDCS. This suggests that prefrontal NBS could affect the emotional response to a threat or challenge rather than affecting emotional state by itself. Hence, prefrontal NBS may modify processes that are involved in changing the emotional state, rather than directly affecting 'static' emotional experience. Prefrontal NBS effects on emotional reactivity could be a result of effects on processes involved in emotion regulation. This is supported by a number of studies showing that anodal tDCS over the PFC mainly facilitates the cognitive modulation of emotions. For example, when participants were instructed to up- or downregulate emotional experience, anodal tDCS enhanced or reduced emotional reactions specifically in the instructed direction[153–155]. In addition, tDCS may primarily affect attentional processes associated with the emotional experience[156]. Such results fit in with the previously proposed idea that prefrontal NBS modulates affective symptoms by improving the ability to self-regulate emotions through enhanced working memory and other cognitive control processes[163–165]. However, this NBS effect on emotion regulation is not always found in single-session NBS studies (see e.g., the study of Jansen and colleagues (2019)[126]). Conclusions

about the effect of NBS on emotion regulation are beyond the scope of the present results, and this hypothesis should be further tested in future studies.

Of the NBS techniques considered in the present article, RTMS and tDCS, it is relatively unexpected that rTMS shows the most uncertain effects. rTMS and tDCS differ in their primary neurophysiological effects, focality and other factors[42,166]. Clinical effects in affective disorders such as depression are more established for rTMS[52,54] than for tDCS[69], and effects on physiological stress reactivity are higher for prefrontal rTMS than for prefrontal tDCS[83]. However, fewer rTMS studies than tDCS studies on emotional stress reactivity were available for the present analyses. Many single-session rTMS studies were not eligible for the current analyses because no experimental stress induction was applied or because emotions were not measured within the time frame of acute rTMS effects. Of the rTMS studies that did measure emotional reactivity, some findings suggest that the acute outcome of rTMS depends on task instructions, rTMS settings or psychological state[127,128,132]. Other rTMS studies did not report any significant effects of a single rTMS session. Lack of acute rTMS effects on emotional reactivity may also be related to timing; tDCS studies often induced the stress or measured the emotional outcome during stimulation, whereas in rTMS studies these procedures usually take place after the stimulation is finished. Moreover, although the research objectives overlapped among the rTMS studies, the number of studies that used the same rTMS methods was limited. The heterogeneity in applied rTMS methods raises an issue concerning the aggregation of their results. The present results should therefore be considered as work in progress, and indicative for the dependence of rTMS effects on various technical, contextual and task-related factors. The influence of such factors should be further investigated before drawing definitive conclusions about the overall effectiveness of rTMS in modulating emotional stress reactivity. On the other hand, the present results also suggest that anodal tDCS might complement rTMS as a technique to modulate stress-related processes. If rTMS and tDCS would eventually yield comparable results in clinical applications, tDCS might be preferred over rTMS for its easier use, portability, and lower costs[166,167].

The evidence for cathodal tDCS effects on subjective stress-related emotions is sparse. Perhaps, cathodal tDCS has low effectivity in general. Little support for significant effects of cathodal tDCS is in line with previous findings of tDCS effects on neural excitability[168] and on cognitive functions[169]. Yet, cathodal tDCS may affect neural excitability and plasticity in opposing ways depending on current intensity and stimulation time[170]. To provide clearer insight in cathodal tDCS, it could be interesting to investigate how these stimulation settings may moderate stimulation effects on emotion- and stress-related processes.

With regard to the optimal target hemisphere for prefrontal NBS, previous research showed that left-sided and right-sided PFC stimulation can have different effects on brain networks involved in emotion regulation and emotional state[171,172], but our results did not demonstrate a clear influence of target hemisphere (left PFC vs. right PFC) on NBS effects at the level of emotional stress reactivity. This is somewhat surprising, since NBS should modulate neural

activity primarily in the target hemisphere, and the data in this review was restricted to negative emotional states that have been associated with asymmetric prefrontal activation. Negative and predominantly withdrawal-related emotions such as fear, nervousness and sadness, are associated with greater right- than left-sided PFC activity[173–177]. In addition, greater right-sided PFC activity has been linked to stronger physiological reactivity to stress[176,178–181], anxiety and depression[173,182,183]. Greater left-sided PFC activity, on the other hand, is linked to stronger approach-related emotional reactions such as enthusiasm[173,178,184], weaker physiological reactivity to stress[176] and reduced emotional reactivity to PTSD symptom provocation[185]. However, greater relative left-sided PFC activity has also been associated with stronger feelings of anger and stronger aggressive responses to stress[173,186,187]. In line with this latter effect of left-sided prefrontal dominance, the tDCS studies of Hortensius and colleagues (2012)[159] and Kelley and colleagues (2015)[160] report increased approach-related emotional reactivity (measured as feelings of anger and jealousy) specifically after applying anodal tDCS to the left PFC and cathodal tDCS to the right DLPFC, but not when the electrode montage was reversed. However, our quantitative results overall do not provide evidence supporting the acute influence of tDCS or rTMS on frontal asymmetry effects on global emotional stress reactivity. The optimal choice of target hemisphere for NBS protocols to modulate emotional processes may depend on other stimulation-related factors such as pulse frequency or current polarity (see also the discussion by Vicario and colleagues[65]). Regarding specific PFC targets, the overview of included studies on emotional reactivity does not show a clear difference between effectivity of NBS over different PFC target regions, and the limited amount of data available per PFC target region prevented meaningful comparisons between target regions. Moreover, when aggregating across studies, the regional specificity of NBS can be low because different localizing methods to target a specific region are used, the electrical field distribution is influenced by individual anatomy, and, especially in case of tDCS, the induced electrical field is not very focal and depends on the electrode montage. Therefore, in the absence of simulations or other measurements of the peak location of the electrical field, we considered it more appropriate to collapse the outcomes from NBS studies targeting various PFC regions. However, targeting different PFC regions may affect different processes and thereby have different effects on stress responses and emotions. To determine the optimal target site for NBS effects on stress- and emotion-related outcomes, more specific comparisons between NBS target regions based on electrical field distributions are needed.

We also considered differences between NBS effects on emotional reactivity across three types of stress: passive stress inductions, psychosocial stress and aversive physical or auditory stress. Different types of stress can differently activate stress systems and differently affect stress regulation strategies[188–190]. However, both rTMS and tDCS studies did not demonstrate systematic different effects on emotional reactivity across types of stress. It could be that the influence of prefrontal NBS on emotional reactivity is independent of stressor category because some (medial) PFC regions are involved in general emotion regulation across different types of stress[14]. Alternatively, the variability in NBS effects on emotional reactivity may not depend on stress sources, but on additional features of the stressor that partly determine

stress response patterns. These include the unpredictability and uncontrollability of the stressor[99,190] and cognitive appraisals about the stressor[104]. Additionally, the type of emotion induced by the stressor makes a difference; stress responses associated with different types of negative emotions, like fear and sadness, show resemblance but also differ in intensity and specific activation patterns, such as shown for amygdala activation, sympathetic nervous system activations, and feelings of pleasantness and arousal[108–110]. Some included emotional outcomes reported in the studies may also be relatively specific to the stress manipulation. It could be difficult to generalize such outcomes to emotional stress reactivity in other situations or to stress-related clinical symptoms. For example, NBS effects on anger after psychosocial stress may say more about potential NBS effects on symptoms of interpersonal distress than on symptoms of panic. However, more research on this topic is needed to be able to zoom in on NBS effects on emotion- or stressor-specific processes. This review combines outcomes of different stress manipulations to give an indication of NBS effects on global emotional reactivity.

Our findings show preliminary evidence that prefrontal NBS, at least with anodal tDCS, lowers acute emotional stress reactivity. This motivates further research in the direction of using prefrontal NBS in enhancing resilience to acute effects of stress. Such protective effects of anodal tDCS have already been show for acute stress interference on cognitive performance[139,146]. If the efficacy of anodal tDCS on emotional reactivity would be further developed, it may be used to attenuate the tendency to strongly react with negative emotions to daily stressors[10], and thereby reduce daily negative affect and the risk on anxiety, chronic stress complaints and PTSD[191–193]. Finally, although speculative, specifically targeting the PFC might improve resilience to the detrimental results of early-life adversity or life stress on PFC structure and function[194,195].

However, beside acute emotional stress reactions, a second important feature is the 'shut-off' or recovery of the stress response once a threat has passed[1]. Future NBS research should therefore continue measuring emotion for a prolonged time after the stress induction, to provide more insight in NBS effects in different stages of the emotional stress response, including the recovery of emotional stress responses.

Moreover, the presently estimated effect size of single NBS sessions in a non-clinical population is small[196]. An effect size of small magnitude in healthy samples agrees with NBS effects on working memory and autonomic nervous system functioning[83,105]. This may be due to a ceiling effect of NBS outcomes when performance on a function is already sufficient[197–200]. Also, because prefrontal NBS effects show intra-individual variability as well as inter-individual variability, NBS may not always affect emotional reactivity in the same manner in all individuals; factors that could influence the strength and direction of NBS effects on PFC-related processes include baseline neural activity[201,202], stress sensitivity[132,142], fatigue, task motivation, and gender[203]. The different NBS methods, participants and experimental

contexts that were used in the included studies could therefore have induced heterogeneous effects on emotional reactivity, which may diminish the summary effect.

Still, across studies, the present findings show a weak effect of a single tDCS session on acute emotion stress reactivity. This effect stimulates to further investigate how the effectiveness of prefrontal tDCS, or NBS in general, can be augmented in order to establish clinically significant effects on emotional stress reactivity. The first and perhaps most obvious way to augment effectiveness is by giving a sequence of multiple stimulation sessions instead of relying on single stimulation sessions. Sequences of multiple stimulation sessions augment NBS effects on neurophysiology[204–208] as well as on behavior, including effects on working memory[209] and cognitive control[210]. Moreover, for therapeutic use in affective disorders, a sequence of 20-30 sessions is recommended[211].

Furthermore, the NBS sessions should be combined with a task that activates or trains the targeted neural process. It has been proposed that the effects of tDCS are largest in neural networks and cognitive functions that are activated or trained during stimulation[212–216], perhaps because synaptic activity could be a prerequisite for NBS effects to occur[217]. NBS effects may even be specific to the activated neural or cognitive process during stimulation. For example, prefrontal tDCS may not have one-directional effects on attentional bias for threat, but when participants are trained to direct attention either towards or away from threat, tDCS specifically increases the attentional bias convergent with the trained direction[218,219]. Also for other cognitive functions, combining prefrontal tDCS with cognitive training amplifies stimulation effects[220], resulting in cognitive benefits that can last for weeks or months and that can transfer to non-trained cognitive skills[210,221]. Likewise, combining prefrontal NBS with cognitive behavioral therapy[222] augments treatment response in depression, PTSD and anxiety disorders[56,71,223–225], while prefrontal NBS in rest (i.e., NBS by itself) does not produce lasting improvements in cognitive performance in neuropsychiatric patients[226,227]. This suggests that NBS effects on emotion regulation processes can be augmented by applying prefrontal NBS during cognitive practice or cognitive therapy.

Finally, although the results of our study suggest that raising stress levels in an experiment may increase the sensitivity of emotional measures to prefrontal NBS effects, it remains unclear whether raising stress levels would also augment prefrontal NBS effects on stress- and emotion-related processes. Some studies showed improved PTSD symptom reduction when prefrontal NBS was combined with trauma exposure[71,228,229], suggesting that NBS can act specifically on the activated fear memory processes. However, single-session NBS studies on fear extinction in healthy individuals[129,157,230–233] and phobia patients[234] have shown null-results or divergent effects of NBS. Further, the effects of a single session of prefrontal NBS on cognitive performance can be similar across neutral and emotionally arousing experimental contexts[235,236], both in depressed and healthy participants[237]. Hence, single-session NBS studies do not clearly demonstrate whether or not prefrontal NBS effectivity depend on stress or arousal levels during NBS. In therapeutic uses of NBS, further studies are needed

to discover if stress levels influence the effects of NBS on stress reactivity and stress-related symptomatology.

FUTURE DIRECTIONS

This study presents an interim overview of the current evidence regarding the direct effects of a number of NBS methods on acute emotional stress reactivity. In this field of research, NBS is often applied with the objective to simply increase or decrease activity in a brain area in order to change stress- or emotion-related outcomes. Yet, our findings show that NBS effects on stress- and emotion-related processes vary. To further clarify the possibilities and limitations of NBS with regard to emotional stress reactivity, future research should focus on a number of important factors.

First of all, the stress processes that are most sensitive to prefrontal NBS should be identified. For instance, physiological measures, including heart rate variability and cortisol responses, appear more sensitive to the acute effects of NBS than self-reports of emotional state[75,83,123,133,147,151,154,238–240]. Possibly, the physiological stress system mediates the effects of NBS on emotional state by lowering bodily arousal, thereby lowering the subjective experience of arousal[241,242], although the subjective arousal outcomes covered in this review did not clearly show stronger NBS effects than other outcomes. Emotional reactivity based on dimensions of valence, arousal or motivational direction also shows a stronger link to physiological stress reactivity than self-report data of discrete emotions[103]. Self-reports of discrete emotions are subject to many other influences, including emotion vocabulary[243] and personality characteristics[244]. On the other hand, some argue that self-reports of discrete emotion categories better capture emotional experiences, because they may have more semantic value[245]. Different measures may thus capture different aspects of emotional experience. Yet, there are also substantial correlations between valence and arousal ratings on one hand, and self-reports of discrete emotions on the other[245–247], suggesting that these different measures capture similar aspects of emotion too. For this reason, different measures of emotional experience have been combined in the present study. To better understand how NBS affects different aspects of emotional experience, future studies should make more explicit distinctions between different measures of dimensional and discrete emotional categories. This difference between measures also demonstrates the need to use measurement instruments that are sensitive to the effects of NBS. For example, a single session of prefrontal NBS may have little effect on global mood after an experiment[72], but could at the same time change the acute emotional response to aversive pictures during the experiment[144,154,155]. In addition, subjective experiences of emotion ('self-focused' emotions) share features with perceptions of emotional stimuli ('world-focused' emotions)[111], but also refer to distinct aspects of emotional processes. The prefrontal cortex, for example, seems more involved in self-focused emotional reactivity[248], suggesting that the focus of the emotional measure may influence sensitivity to prefrontal NBS effects. The use of insensitive measurement instruments or measurement timings may introduce heterogeneity in the outcomes and thereby obscure the direct effects of NBS.

Second, acute NBS effects seem to depend on task or experimental settings, such as task instructions[128,153–155], the relationship between the emotion and the behavior that is induced by the stressor[159,160], and time between the stress induction and measuring the emotional outcome[144,154,157]. Future NBS research should pay attention to experimental tasks and measurement protocols that are sensitive to the NBS effects, especially in single session NBS experiments that produce very subtle effects.

Third, preferred cortical targets for NBS applications in stress and emotion may lie beyond the PFC. For example, stimulating the dorsal anterior cingulate cortex (dACC) could enhance emotional learning and memory for extinction of fear memories[163,249]. Yet, the dACC may lie out of reach for tDCS and conventional rTMS, and might therefore better be targeted by techniques such as deep TMS[228,250,251]. In addition, the occipital cortex[252], the parietal cortex[253,254], and the cerebellum[255,256] may be suitable NBS targets to improve emotion regulation or restore emotional perception deficits in affective disorders[257].

Fourth, applying rTMS in certain rhythmic patterns or using transcranial alternate current stimulation (tACS) can induce interaction with other components of brain function than conventional rTMS and tDCS, e.g., by influencing ongoing oscillatory activity[258–260]. Such techniques may provide an alternative pathway to modulate cortical excitability[258] and cognitive functions like working memory[261].

Finally, NBS effects are shaped by many technical[169,262–266], biological[202,267–271], clinical[272], and personal factors[166,273–275]. However, the data in the present quantitative analysis did not allow analyses of all these factor-specific effects. Accordingly, the estimated effect sizes in this work might not be applicable to specific methods or populations. Future research should determine if and how moderating factors shape the scope of prefrontal NBS effects, particularly those moderating factors that are relevant to stress and emotion.

CONCLUSION

This review and quantitative analysis presents an overview of the direct effects of single-session prefrontal NBS on emotional stress reactivity as investigated with various NBS methods. These studies together do not provide evidence for a one-directional effect of prefrontal NBS on emotional stress reactivity in healthy individuals. However, the magnitude and direction of NBS effects on emotional reactivity may depend on various technical, experimental, neurobiological and mental state factors, which prevents drawing definite conclusions about the overall direct effects of prefrontal NBS on stress-related emotions. Effects of specific NBS methods demonstrate a small beneficial effect on emotional stress reactivity of anodal tDCS. These preliminary findings imply that prefrontal NBS can potentially be used to facilitate resilience against the detrimental impact of stress on cognitive functioning and mental health, but only if this technique is further investigated and developed.

DECLARATION OF INTEREST

The authors declare no conflicts of interest.

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REFERENCES

1. McEwen BS. Stress, Adaptation, and Disease: Allostasis and Allostatic Load. *Ann N Y Acad Sci*. 1998;840(1):33-44. doi:10.1111/j.1749-6632.1998.tb09546.x

2. Shields GS, Sazma MA, Yonelinas AP. The effects of acute stress on core executive functions: A meta-analysis and comparison with cortisol. *Neuroscience & Biobehavioral Reviews*. 2016;68:651-668. doi:10.1016/j.neubiorev.2016.06.038

3. Arora S, Sevdalis N, Nestel D, Woloshynowych M, Darzi A, Kneebone R. The impact of stress on surgical performance: A systematic review of the literature. *Surgery*. 2010;147(3):318-330.e6. doi:10.1016/j.surg.2009.10.007

4. Chrouser KL, Xu J, Hallbeck S, Weinger MB, Partin MR. The influence of stress responses on surgical performance and outcomes: Literature review and the development of the surgical stress effects (SSE) framework. *The American Journal of Surgery*. 2018;216(3):573-584. doi:10.1016/j.amjsurg.2018.02.017

5. Regehr C, LeBlanc VR. PTSD, Acute Stress, Performance and Decision-Making in Emergency Service Workers. *J Am Acad Psychiatry Law*. 2017;45(2):184-192.

6. Harris WC, Hancock PA, Harris SC. Information Processing Changes Following Extended Stress. *Military Psychology*. 2005;17(2):115-128. doi:10.1207/s15327876mp1702_4

7. Orasanu JM, Backer P. Stress and military performance. In: *Stress and Human Performance*. Erlbaum; 1996:89-125.

8. McLaughlin KA, Kubzansky LD, Dunn EC, Waldinger R, Vaillant G, Koenen KC. Childhood social environment, emotional reactivity to stress, and mood and anxiety disorders across the life course. *Depression and Anxiety*. 2010;27(12):1087-1094. doi:10.1002/da.20762

9. Swartz JR, Knodt AR, Radtke SR, Hariri AR. A neural biomarker of psychological vulnerability to future life stress. *Neuron*. 2015;85(3):505-511. doi:10.1016/j.neuron.2014.12.055

10. Charles ST, Piazza JR, Mogle J, Sliwinski MJ, Almeida DM. The Wear and Tear of Daily Stressors on Mental Health. *Psychological Science*. 2013;24(5):733-741. doi:10.1177/0956797612462222

11. Radley J, Morilak D, Viau V, Campeau S. Chronic stress and brain plasticity: Mechanisms underlying adaptive and maladaptive changes and implications for stress-related CNS disorders. *Neuroscience and Biobehavioral Reviews*. Published online 2015. doi:10.1016/j.neubiorev.2015.06.018

12. Kim MJ, Loucks R a., Palmer AL, et al. The structural and functional connectivity of the amygdala: From normal emotion to pathological anxiety. *Behavioural Brain Research*. 2011;223(2):403-410. doi:10.1016/j.bbr.2011.04.025

13. Diorio D, Viau V, Meaney MJ. The role of the medial prefrontal cortex (cingulate gyrus) in the regulation of hypothalamic-pituitary-adrenal responses to stress. *Journal of Neuroscience*. Published online 1993.

14. Diekhof EK, Geier K, Falkai P, Gruber O. Fear is only as deep as the mind allows. *Neuroimage*. 2011;58(1):275-285. doi:10.1016/j.neuroimage.2011.05.073

15. Phillips ML, Drevets WC, Rauch SL, Lane R. Neurobiology of emotion perception I: the neural basis of normal emotion perception. *Biological Psychiatry*. 2003;54(5):504-514. doi:10.1016/S0006-3223(03)00168-9

16. Steele JD, Lawrie SM. Segregation of cognitive and emotional function in the prefrontal cortex: A stereotactic meta-analysis. *Neuroimage*. 2004;21(3):868-875. doi:10.1016/j.neuroimage.2003.09.066

17. Ochsner KN, Silvers JA, Buhle JT. Functional imaging studies of emotion regulation: a synthetic review and evolving model of the cognitive control of emotion. *Ann N Y Acad Sci*. 2012;1251(1):E1-E24. doi:10.1111/j.1749-6632.2012.06751.x

18. Etkin A, Büchel C, Gross JJ. The neural bases of emotion regulation. *Nature Reviews Neuroscience*. 2015;16(11):693-700. doi:10.1038/nrn4044

19. Kohn N, Eickhoff SB, Scheller M, Laird AR, Fox PT, Habel U. Neural network of cognitive emotion regulation — An ALE meta-analysis and MACM analysis. *Neuroimage*. 2014;87:345-355. doi:10.1016/j.neuroimage.2013.11.001

20. Wager TD, Davidson ML, Hughes BL, Lindquist MA, Ochsner KN. Prefrontal-Subcortical Pathways Mediating Successful Emotion Regulation. *Neuron*. 2008;59(6):1037-1050. doi:10.1016/j.neuron.2008.09.006

21. Buhle JT, Silvers JA, Wager TD, et al. Cognitive Reappraisal of Emotion: A Meta-Analysis of Human Neuroimaging Studies. *Cerebral Cortex*. 2014;24(11):2981-2990. doi:10.1093/cercor/bht154

22. Morawetz C, Bode S, Derntl B, Heekeren HR. The effect of strategies, goals and stimulus material on the neural mechanisms of emotion regulation: A meta-analysis of fMRI studies. *Neuroscience & Biobehavioral Reviews*. 2017;72:111-128. doi:10.1016/j.neubiorev.2016.11.014

23. Langner R, Leiberg S, Hoffstaedter F, Eickhoff SB. Towards a human self-regulation system: Common and distinct neural signatures of emotional and behavioural control. *Neuroscience & Biobehavioral Reviews*. 2018;90:400-410. doi:10.1016/j.neubiorev.2018.04.022

24. Arnsten AFT. Stress weakens prefrontal networks: molecular insults to higher cognition. *Nature Neuroscience*. 2015;18(10):1376-1385. doi:10.1038/nn.4087

25. McEwen BS, Morrison JH. The Brain on Stress: Vulnerability and Plasticity of the Prefrontal Cortex over the Life Course. *Neuron*. 2013;79(1):16-29. doi:10.1016/j.neuron.2013.06.028

26. Via E, Fullana MA, Goldberg X, et al. Ventromedial prefrontal cortex activity and pathological worry in generalised anxiety disorder. *The British Journal of Psychiatry*. 2018;213(1):437-443. doi:10.1192/bjp.2018.65

27. Sylvester CM, Corbetta M, Raichle ME, et al. Functional network dysfunction in anxiety and anxiety disorders. *Trends in Neurosciences*. 2012;35(9):527-535. doi:10.1016/j.tins.2012.04.012

28. Zilverstand A, Parvaz MA, Goldstein RZ. Neuroimaging cognitive reappraisal in clinical populations to define neural targets for enhancing emotion regulation. A systematic review. *Neuroimage*. 2017;151:105-116. doi:10.1016/j.neuroimage.2016.06.009

29. Manber Ball T, Ramsawh HJ, Campbell-Sills L, Paulus MP, Stein MB. Prefrontal dysfunction during emotion regulation in generalized anxiety and panic disorders. *Psychological Medicine*. 2013;43(7):1475-1486. doi:10.1017/S0033291712002383

30. Etkin A, Wager TD. Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. *Am J Psychiatry*. 2007;164(10):1476-1488. doi:10.1176/appi.ajp.2007.07030504

31. Grupe DW, Nitschke JB. Uncertainty and anticipation in anxiety: an integrated neurobiological and psychological perspective. *Nature Reviews Neuroscience*. 2013;14(7):488-501. doi:10.1038/nrn3524

32. Bishop SJ. Neurocognitive mechanisms of anxiety: an integrative account. *Trends in Cognitive Sciences*. 2007;11(7):307-316. doi:10.1016/j.tics.2007.05.008

33. Bishop SJ. Trait anxiety and impoverished prefrontal control of attention. *Nature Neuroscience*. 2009;12(1):92-98. doi:10.1038/nn.2242

34. Basten U, Stelzel C, Fiebach CJ. Trait Anxiety Modulates the Neural Efficiency of Inhibitory Control. *Journal of Cognitive Neuroscience*. 2011;23(10):3132-3145. doi:10.1162/jocn_a_00003

35. Harmer CJ, Mackay CE, Reid CB, Cowen PJ, Goodwin GM. Antidepressant Drug Treatment Modifies the Neural Processing of Nonconscious Threat Cues. *Biological Psychiatry*. 2006;59(9):816-820. doi:10.1016/j.biopsych.2005.10.015

36. MacNamara A, Rabinak CA, Kennedy AE, et al. Emotion Regulatory Brain Function and SSRI Treatment in PTSD: Neural Correlates and Predictors of Change. *Neuropsychopharmacology*. 2016;41(2):611-618. doi:10.1038/npp.2015.190

37. Schweizer S, Grahn J, Hampshire A, Mobbs D, Dalgleish T. Training the Emotional Brain: Improving Affective Control through Emotional Working Memory Training. *Journal of Neuroscience*. 2013;33(12):5301-5311. doi:10.1523/JNEUROSCI.2593-12.2013

38. Browning M, Holmes EA, Murphy SE, Goodwin GM, Harmer CJ. Lateral Prefrontal Cortex Mediates the Cognitive Modification of Attentional Bias. *Biological Psychiatry*. 2010;67(10):919-925. doi:10.1016/j.biopsych.2009.10.031

39. Carlisi CO, Robinson OJ. The role of prefrontal–subcortical circuitry in negative bias in anxiety: Translational, developmental and treatment perspectives. *Brain and Neuroscience Advances*. 2018;2:239821281877422. doi:10.1177/2398212818774223

40. Goldin PR, Ziv M, Jazaieri H, Weeks J, Heimberg RG, Gross JJ. Impact of cognitive-behavioral therapy for social anxiety disorder on the neural bases of emotional reactivity to and regulation of social evaluation. *Behaviour Research and Therapy*. 2014;62:97-106. doi:10.1016/j.brat.2014.08.005

41. Cirillo G, di Pino G, Capone F, et al. Neurobiological after-effects of non-invasive brain stimulation. *Brain Stimulation*. 2017;10(1):1-18. doi:10.1016/j.brs.2016.11.009

42. Dayan E, Censor N, Buch ER, Sandrini M, Cohen LG. Noninvasive brain stimulation: from physiology to network dynamics and back. *Nat Neurosci*. 2013;16(7):838-844. doi:10.1038/nn.3422

43. Fitzgerald P, Fountain S, Daskalakis Z. A comprehensive review of the effects of rTMS on motor cortical excitability and inhibition. *Clinical Neurophysiology*. 2006;117(12):2584-2596. doi:10.1016/j.clinph.2006.06.712

44. Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta Burst Stimulation of the Human Motor Cortex. *Neuron*. 2005;45(2):201-206. doi:10.1016/j.neuron.2004.12.033

45. Wischnewski M, Schutter DJLG. Efficacy and time course of theta burst stimulation in healthy humans. *Brain Stimulation*. 2015;8(4):685-692. doi:10.1016/j.brs.2015.03.004

46. Gamboa OL, Antal A, Moliadze V, Paulus W. Simply longer is not better: reversal of theta burst after-effect with prolonged stimulation. *Exp Brain Res*. 2010;204(2):181-187. doi:10.1007/s00221-010-2293-4

47. Duecker F, Sack AT. Rethinking the role of sham TMS. *Frontiers in Psychology*. 2015;6:210. doi:10.3389/fpsyg.2015.00210

48. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *The Journal of Physiology*. 2000;527(3):633-639. doi:10.1111/j.1469-7793.2000.t01-1-00633.x

49. Liebetanz D. Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability. *Brain*. 2002;125(10):2238-2247. doi:10.1093/brain/awf238

50. Ambrus GG, Al-Moyed H, Chaieb L, Sarp L, Antal A, Paulus W. The fade-in – Short stimulation – Fade out approach to sham tDCS – Reliable at 1 mA for naïve and experienced subjects, but not investigators. *Brain Stimulation*. 2012;5(4):499-504. doi:10.1016/j.brs.2011.12.001

51. Shafi MM, Westover MB, Fox MD, Pascual-Leone A. Exploration and modulation of brain network interactions with noninvasive brain stimulation in combination with neuroimaging. *European Journal of Neuroscience*. 2012;35(November 2011):805-825. doi:10.1111/j.1460-9568.2012.08035.x

52. Berlim MT, Van den Eynde F, Daskalakis ZJ. A systematic review and meta-analysis on the efficacy and acceptability of bilateral repetitive transcranial magnetic stimulation (rTMS) for treating major depression. *Psychol Med*. 2013;43(11):2245-2254. doi:10.1017/S0033291712002802

53. Gaynes BN, Lloyd SW, Lux L, et al. Repetitive transcranial magnetic stimulation for treatment-resistant depression: a systematic review and meta-analysis. *The Journal of Clinical Psychiatry*. 2014;75(5):477-489; quiz 489. doi:10.4088/JCP.13r08815

54. Schutter DJLG. Quantitative review of the efficacy of slow-frequency magnetic brain stimulation in major depressive disorder. *Psychological Medicine*. 2010;40(11):1789-1795. doi:10.1017/S003329171000005X

55. Berlim MT, van den Eynde F, Tovar-Perdomo S, Daskalakis ZJ. Response, remission and drop-out rates following high-frequency repetitive transcranial magnetic stimulation (rTMS) for treating major depression: a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. *Psychological Medicine*. 2014;44(02):225-239. doi:10.1017/S0033291713000512

56. Kozel FA, Motes MA, Didehbani N, et al. Repetitive TMS to augment cognitive processing therapy in combat veterans of recent conflicts with PTSD: A randomized clinical trial. *Journal of Affective Disorders*. 2018;229:506-514. doi:10.1016/j.jad.2017.12.046

57. Philip NS, Ridout SJ, Albright SE, Sanchez G, Carpenter LL. 5-Hz Transcranial Magnetic Stimulation for Comorbid Posttraumatic Stress Disorder and Major Depression. *Journal of Traumatic Stress*. 2016;29(1):93-96. doi:10.1002/jts.22065

58. Berlim MT, Van den Eynde F. Repetitive Transcranial Magnetic Stimulation Over the Dorsolateral Prefrontal Cortex for Treating Posttraumatic Stress Disorder: An Exploratory Meta-Analysis of Randomized, Double-Blind and Sham-Controlled Trials. *Canadian Journal of Psychiatry*. 2014;59(9):487-496.

59. Ahmadizadeh MJ, Rezaei M. Unilateral right and bilateral dorsolateral prefrontal cortex transcranial magnetic stimulation in treatment post-traumatic stress disorder: A randomized controlled study. *Brain Research Bulletin*. 2018;140(April):334-340. doi:10.1016/j.brainresbull.2018.06.001

60. Boggio PS, Rocha M, Oliveira MO, et al. Noninvasive Brain Stimulation With High-Frequency and Low-Intensity Repetitive Transcranial Magnetic Stimulation Treatment for Posttraumatic Stress Disorder. *The Journal of Clinical Psychiatry*. 2010;71(08):992-999. doi:10.4088/JCP.08m04638blu

61. Diefenbach GJ, Bragdon LB, Zertuche L, et al. Repetitive transcranial magnetic stimulation for generalised anxiety disorder: a pilot randomised, double-blind, sham-controlled trial. *The British Journal of Psychiatry*. 2016;209(3):222-228. doi:10.1192/bjp.bp.115.168203

62. Dilkov D, Hawken ER, Kaludiev E, Milev R. Repetitive transcranial magnetic stimulation of the right dorsal lateral prefrontal cortex in the treatment of generalized anxiety disorder: A randomized, double-blind sham controlled clinical trial. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2017;78:61-65. doi:10.1016/j.pnpbp.2017.05.018

63. Assaf M, Rabany L, Zertuche L, et al. Neural functional architecture and modulation during decision making under uncertainty in individuals with generalized anxiety disorder. *Brain and Behavior*. Published online June 21, 2018:e01015. doi:10.1002/brb3.1015

64. Mantovani A, Aly M, Dagan Y, Allart A, Lisanby SH. Randomized sham controlled trial of repetitive transcranial magnetic stimulation to the dorsolateral prefrontal cortex for the treatment of panic disorder with comorbid major depression. *Journal of Affective Disorders*. 2013;144(1-2):153-159. doi:10.1016/j.jad.2012.05.038

65. Vicario CM, Salehinejad MA, Felmingham K, Martino G, Nitsche MA. A systematic review on the therapeutic effectiveness of non-invasive brain stimulation for the treatment of anxiety disorders. *Neuroscience and Biobehavioral Reviews*. 2019;96(August 2018):219-231. doi:10.1016/j.neubiorev.2018.12.012

66. Deppermann S, Vennewald N, Diemer J, et al. Does rTMS Alter Neurocognitive Functioning in Patients with Panic Disorder/Agoraphobia? An fNIRS-Based Investigation of Prefrontal Activation during a Cognitive Task and Its Modulation via Sham-Controlled rTMS. *BioMed Research International*. 2014;2014:1-12. doi:10.1155/2014/542526

67. Prasko J, Záleský R, Bares M, et al. The effect of repetitive transcranial magnetic stimulation (rTMS) add on serotonin reuptake inhibitors in patients with panic disorder: a randomized, double blind sham controlled study. *Neuro Endocrinol Lett*. 2007;28(1):33-38.

68. Yan T, Xie Q, Zheng Z, Zou K, Wang L. Different frequency repetitive transcranial magnetic stimulation (rTMS) for posttraumatic stress disorder (PTSD): A systematic review and meta-analysis. *Journal of Psychiatric Research*. 2017;89:125-135. doi:10.1016/j.jpsychires.2017.02.021

69. Shiozawa P, Fregni F, Benseñor IM, et al. Transcranial direct current stimulation for major depression: an updated systematic review and meta-analysis. *The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharma-cologicum (CINP)*. 2014;17(9):1443-1452. doi:10.1017/S1461145714000418

70. Ahmadizadeh MJ, Rezaei M, Fitzgerald PB. Transcranial direct current stimulation (tDCS) for post-traumatic stress disorder (PTSD): A randomized, double-blinded, controlled trial. *Brain Research Bulletin*. 2019;153(September):273-278. doi:10.1016/j.brainresbull.2019.09.011

71. van 't Wout-Frank M, Shea MT, Larson VC, Greenberg BD, Philip NS. Combined transcranial direct current stimulation with virtual reality exposure for posttraumatic stress disorder: Feasibility and pilot results. *Brain Stimulation*. 2019;12(1):41-43. doi:10.1016/j.brs.2018.09.011

72. Remue J, Baeken C, de Raedt R. Does a single neurostimulation session really affect mood in healthy individuals? A systematic review. *Neuropsychologia*. 2016;85:184-198. doi:10.1016/j.neuropsychologia.2016.03.012

73. Preston G, Anderson E, Silva C, Goldberg T, Wassermann EM. Effects of 10 Hz rTMS on the Neural Efficiency of Working Memory. *Journal of Cognitive Neuroscience*. 2010;22(3):447-456. doi:10.1162/jocn.2009.21209

74. Bagherzadeh Y, Khorrami A, Zarrindast MR, Shariat SV, Pantazis D. Repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex enhances working memory. *Experimental Brain Research*. 2016;234(7):1807-1818. doi:10.1007/s00221-016-4580-1

75. Brunoni AR, Vanderhasselt MA, Boggio PS, et al. Polarity- and valence-dependent effects of prefrontal transcranial direct current stimulation on heart rate variability and salivary cortisol. *Psychoneuroendocrinology*. 2013;38(1):58-66. doi:10.1016/j.psyneuen.2012.04.020

76. Mondino M, Thiffault F, Fecteau S. Does non-invasive brain stimulation applied over the dorsolateral prefrontal cortex non-specifically influence mood and emotional processing in healthy individuals? *Front Cell Neurosci*. 2015;9(October):399. doi:10.3389/fncel.2015.00399

77. Zwanzger P, Fallgatter AJ, Zavorotnyy M, Padberg F. Anxiolytic effects of transcranial magnetic stimulation—an alternative treatment option in anxiety disorders? *Journal of Neural Transmission*. 2009;116(6):767-775. doi:10.1007/s00702-008-0162-0

78. Kuo MF, Nitsche MA. Exploring prefrontal cortex functions in healthy humans by transcranial electrical stimulation. *Neuroscience Bulletin*. 2015;31(2):198-206. doi:10.1007/s12264-014-1501-9

79. Levasseur-Moreau J, Fecteau S. Translational application of neuromodu-lation of decision-making. *Brain Stimulation*. 2012;5(2):77-83. doi:10.1016/j.brs.2012.03.009

80. Balconi M. Dorsolateral prefrontal cortex, working memory and episodic memory processes: insight through transcranial magnetic stimulation techniques. *Neuroscience Bulletin*. 2013;29(3):381-389. doi:10.1007/s12264-013-1309-z

81. Bell SB, DeWall N. Does transcranial direct current stimulation to the prefrontal cortex affect social behavior? A meta-analysis. *Social Cognitive and Affective Neuroscience*. 2018;13(9):899-906. doi:10.1093/scan/nsy069

82. Nitsche MA, Koschack J, Pohlers H, Hullemann S, Paulus W, Happe S. Effects of frontal transcranial direct current stimulation on emotional state and processing in healthy humans. *Front Psychiatry*. 2012;3:58. doi:10.3389/fpsyt.2012.00058

83. Makovac E, Thayer JF, Ottaviani C. A meta-analysis of non-invasive brain stimulation and autonomic functioning: Implications for brain-heart pathways to cardiovascular disease. *Neuroscience & Biobehavioral Reviews*. 2017;74:330-341. doi:10.1016/j.neubiorev.2016.05.001

84. Kirschbaum C, Pirke KM, Hellhammer DH. The 'Trier Social Stress Test' – A Tool for Investigating Psychobiological Stress Responses in a Laboratory Setting. *Neuropsychobiology*. 1993;28(1-2):76-81. doi:https://doi.org/10.1159/000119004

85. Williams KD, Cheung CKT, Choi W. Cyberostracism: Effects of being ignored over the internet. *Journal of Personality and Social Psychology*. Published online 2000. doi:10.1037/0022-3514.79.5.748

86. Gerdes ABM, Wieser MJ, Mühlberger A, et al. Brain activations to emotional pictures are differentially associated with valence and arousal ratings. *Frontiers in Human Neuroscience*. Published online 2010. doi:10.3389/fnhum.2010.00175

87. Bernat E, Patrick CJ, Benning SD, Tellegen A. Effects of picture content and intensity on affective physiological response. *Psychophysiology*. Published online 2006. doi:10.1111/j.1469-8986.2006.00380.x

88. Lang PJ, Greenwald MK, Bradley MM, Hamm AO. Looking at pictures: Affective, facial, visceral, and behavioral reactions. *Psychophysiology*. 1993;30(3):261-273. doi:10.1111/j.1469-8986.1993.tb03352.x

89. Allen AP, Kennedy PJ, Cryan JF, Dinan TG, Clarke G. Biological and psychological markers of stress in humans: Focus on the Trier Social Stress Test. *Neuroscience and Biobehavioral Reviews*. Published online 2014. doi:10.1016/j.neubiorev.2013.11.005

90. Boyes ME, French DJ. Having a Cyberball: Using a ball-throwing game as an experimental social stressor to examine the relationship between neuroticism and coping. *Personality and Individual Differences*. Published online 2009. doi:10.1016/j.paid.2009.04.005

91. Zadro L, Williams KD, Richardson R. How low can you go? Ostracism by a computer is sufficient to lower self-reported levels of belonging, control, self-esteem, and meaningful existence. *Journal of Experimental Social Psychology*. Published online 2004. doi:10.1016/j.jesp.2003.11.006

92. Kelly M, McDonald S, Rushby J. All alone with sweaty palms - Physiological arousal and ostracism. *International Journal of Psychophysiology*. Published online 2012. doi:10.1016/j.ijpsycho.2011.11.008

93. Storm H, Günther A, Sackey PV, Bernhardsson J, Bjärtå A. Measuring pain—Physiological and self-rated measurements in relation to pain stimulation and anxiety. *Acta Anaesthesiologica Scandinavica*. Published online 2019. doi:10.1111/aas.13323

94. Lipp O V. Human fear learning: Contemporary procedures and measure-ment. In: *Fear and Learning: From Basic Processes to Clinical Implications*. ; 2006:37-51.

95. van Stegeren AH, Wolf OT, Kindt M. Salivary alpha amylase and cortisol responses to different stress tasks: Impact of sex. *International Journal of Psychophysiology*. Published online 2008. doi:10.1016/j.ijpsycho.2008.02.008

96. Sijtsema JJ, Shoulberg EK, Murray-Close D. Physiological reactivity and different forms of aggression in girls: Moderating roles of rejection sensitivity and peer rejection. *Biological Psychology*. Published online 2011. doi:10.1016/j.biopsycho.2010.11.007

97. Maruyama Y, Kawano A, Okamoto S, et al. Differences in salivary alpha-amylase and cortisol responsiveness following exposure to electrical stimulation versus the trier social stress tests. *PLoS ONE*. Published online 2012. doi:10.1371/journal.pone.0039375

98. Helpman L, Penso J, Zagoory-Sharon O, Feldman R, Gilboa-Schechtman E. Endocrine and emotional response to exclusion among women and men; cortisol, salivary alpha amylase, and mood. *Anxiety, Stress and Coping*. Published online 2017. doi:10.1080/10615806.2016.1269323

99. Dickerson SS, Kemeny ME. Acute stressors and cortisol responses: A theoretical integration and synthesis of laboratory research. *Psychological Bulletin*. Published online 2004. doi:10.1037/0033-2909.130.3.355

100. Ottowitz WE, Dougherty DD, Sirota A, Niaura R, Rauch SL, Brown WA. Neural and endocrine correlates of sadness in women: Implications for neural network regulation of HPA activity. *Journal of Neuropsychiatry and Clinical Neurosciences*. Published online 2004. doi:10.1176/jnp.16.4.446

101. Root JC, Tuescher O, Cunningham-Bussel A, et al. Frontolimbic function and cortisol reactivity in response to emotional stimuli. *NeuroReport*. Published online 2009. doi:10.1097/WNR.0b013e328326a031

102. Gadea M, Gómez C, González-Bono E, Espert R, Salvador A. Increased cortisol and decreased right ear advantage (REA) in dichotic listening following a negative mood induction. *Psychoneuroendocrinology*. Published online 2005. doi:10.1016/j.psyneuen.2004.06.005

103. Mauss IB, Robinson MD. Measures of emotion: A review. *Cognition & Emotion*. 2009;23(2):209-237. doi:10.1080/02699930802204677

104. Denson TF, Spanovic M, Miller N. Cognitive Appraisals and Emotions Predict Cortisol and Immune Responses: A Meta-Analysis of Acute Laboratory Social Stressors and Emotion Inductions. *Psychological Bulletin*. Published online 2009. doi:10.1037/a0016909

105. Brunoni AR, Vanderhasselt MA. Working memory improvement with non-invasive brain stimulation of the dorsolateral prefrontal cortex: A systematic review and meta-analysis. *Brain and Cognition*. 2014;86:1-9. doi:10.1016/j.bandc.2014.01.008

106. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews*. 2015;4(1):1. doi:10.1186/2046-4053-4-1

107. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. In: *The Cochrane Collaboration*. ; 2011.

108. Phan KL, Wager T, Taylor SF, Liberzon I. Functional neuroanatomy of emotion: A meta-analysis of emotion activation studies in PET and fMRI. *Neuroimage*. Published online 2002. doi:10.1006/nimg.2002.1087

109. Kreibig SD. Autonomic nervous system activity in emotion: A review. *Biological Psychology*. Published online 2010. doi:10.1016/j.biopsycho.2010.03.010

110. Kreibig SD, Wilhelm FH, Roth WT, Gross JJ. Cardiovascular, electrodermal, and respiratory response patterns to fear- and sadness-inducing films. *Psychophysiology*. Published online 2007. doi:10.1111/j.1469-8986.2007.00550.x

111. Quigley KS, Lindquist KA, Barrett LF. Inducing and Measuring Emotion and Affect: Tips , Tricks , and Secrets. *Handbook of Research Methods in Social and Personality Psychology*. Published online 2013. doi:http://dx.doi.org/10.1017/CBO9780511996481.014

112. Hedges L V. Distribution Theory for Glass's Estimator of Effect size and Related Estimators. *Journal of Educational Statistics*. 1981;6(2):107-128. doi:10.3102/10769986006002107

113. R Foundation for Statistical Computing. R: A language and environment for statistical computing. *R: A Language and Environment for Statistical Computing 331*. Published online 2016.

114. Viechtbauer W. Package 'metafor.' *CRAN*. Published online 2012.

115. Lin L. *Statistical Methods for Meta-Analysis*. Academic Press; 2017.

116. Moeyaert M, Ugille M, Natasha Beretvas S, Ferron J, Bunuan R, Van den Noortgate W. Methods for dealing with multiple outcomes in meta-analysis : a comparison between averaging effect sizes, robust variance estimation and multilevel meta-analysis. *International Journal of Social Research Methodology*. 2017;20(6):559-572. doi:10.1080/13645579.2016.1252189

117. Hedges L V., Tipton E, Johnson MC. Robust variance estimation in meta-regression with dependent effect size estimates. *Research Synthesis Methods*. 2010;1(1):39-65. doi:10.1002/jrsm.5

118. Fisher Z, Tipton E. robumeta: An R-package for robust variance estimation in meta-analysis. *arXiv preprint arXiv:150302220*. Published online 2015.

119. Pustejovsky J. clubSandwich: Cluster-Robust (Sandwich) Variance Estimators with Small-Sample Corrections. *https://CRANR-project.org/package=clubSandwich*. Published online 2018:R package version 0.3.2.

120. Tipton E. Small sample adjustments for robust variance estimation with meta-regression. *Psychological Methods*. 2015;20(3):375-393. doi:10.1037/met0000011

121. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *Journal of Epidemiology & Community Health*. 1998;52(6):377-384. doi:10.1136/jech.52.6.377

122. Hartling L, Hamm M, Mile A, Al. E. Guidelines for Risk of Bias Assessments. In: *Validity and Inter-Rater Reliability Testing of Quality Assessment Instruments, Appendix B [Internet]*. Agency for Healthcare Research and Quality (US); 2012. https://www.ncbi.nlm.nih.gov/books/NBK92290/%0A

123. Baeken C, Vanderhasselt MA, Remue J, et al. One left dorsolateral prefrontal cortical HF-rTMS session attenuates HPA-system sensitivity to critical feedback in healthy females. *Neuropsychologia*. 2014;57:112-121. doi:10.1016/j.neuropsychologia.2014.02.019

124. de Witte S, Baeken C, Pulopulos MM, et al. The effect of neurostimulation applied to the left dorsolateral prefrontal cortex on post-stress adaptation as a function of depressive brooding. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2020;96:109687. doi:10.1016/j.pnpbp.2019.109687

125. Berger C, Domes G, Balschat J, Thome J, Höppner J. Effects of prefrontal rTMS on autonomic reactions to affective pictures. *Journal of Neural Transmission*. 2017;124(S1):139-152. doi:10.1007/s00702-015-1491-4

126. Jansen JM, van den Heuvel OA, van der Werf YD, et al. The effect of high-frequency repetitive transcranial magnetic stimulation on emotion processing, reappraisal, and craving in alcohol use disorder patients and healthy controls: A functional magnetic resonance imaging study. *Frontiers in Psychiatry*. 2019;10:272. doi:10.3389/fpsyt.2019.00272

127. Notzon S, Steinberg C, Zwanzger P, Junghöfer M. Modulating Emotion Perception: Opposing Effects of Inhibitory and Excitatory Prefrontal Cortex Stimulation. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*. 2018;3(4):329-336. doi:10.1016/j.bpsc.2017.12.007

128. Möbius M, Lacomblé L, Meyer T, et al. Repetitive transcranial magnetic stimulation modulates the impact of a negative mood induction. *Soc Cogn Affect Neurosci*. 2017;12(4):526-533. doi:10.1093/scan/nsw180

129. Guhn A, Dresler T, Andreatta M, et al. Medial prefrontal cortex stimulation modulates the processing of conditioned fear. *Front Behav Neurosci*. 2014;8(February):44. doi:10.3389/fnbeh.2014.00044

130. Zwanzger P, Steinberg C, Rehbein MA, et al. Inhibitory repetitive transcranial magnetic stimulation (rTMS) of the dorsolateral prefrontal cortex modulates early affective processing. *Neuroimage*. 2014;101:193-203. doi:10.1016/j.neuroimage.2014.07.003

131. Zwanzger P, Eser D, Völkel N, et al. Effects of repetitive transcranial magnetic stimulation (rTMS) on panic attacks induced by cholecystokinin-tetrapeptide (CCK-4). *The International Journal of Neuropsychopharmacology*. 2007;10(02):285-289. doi:10.1017/S146114570600695X

132. Fitzgibbon BM, Kirkovski M, Bailey NW, et al. Low-frequency brain stimulation to the left dorsolateral prefrontal cortex increases the negative impact of social exclusion among those high in personal distress. *Social Neuroscience*. 2017;12(3):237-241. doi:10.1080/17470919.2016.1166154

133. Hurlemann R, Arndt S, Schlaepfer TE, Reul J, Maier W, Scheele D. Diminished appetitive startle modulation following targeted inhibition of prefrontal cortex. *Scientific Reports*. 2015;5(1):8954. doi:10.1038/srep08954

134. Keuper K, Terrighena EL, Chan CCH, Junghoefer M, Lee TMC. How the Dorsolateral Prefrontal Cortex Controls Affective Processing in Absence of Visual Awareness – Insights From a Combined EEG-rTMS Study. *Frontiers in Human Neuroscience*. 2018;12:412. doi:10.3389/fnhum.2018.00412

135. Voss M, Ehring T, Wolkenstein L. Does Transcranial Direct Current Stimulation Affect Post-stressor Intrusive Memories and Rumination? An Experimental Analogue Study. *Cognitive Therapy and Research*. Published online November 15, 2018:1-15. doi:10.1007/s10608-018-9976-8

136. Deldar Z, Rustamov N, Bois S, Blanchette I, Piché M. Enhancement of pain inhibition by working memory with anodal transcranial direct current stimulation of the left dorsolateral prefrontal cortex. *The Journal of Physiological Sciences*. 2018;68(6):825-836. doi:10.1007/s12576-018-0598-4

137. Vierheilig N, Mühlberger A, Polak T, Herrmann MJ. Transcranial direct current stimulation of the prefrontal cortex increases attention to visual target stimuli. *Journal of Neural Transmission*. 2016;123(10):1195-1203. doi:10.1007/s00702-016-1542-5

138. Baeken C, Dedoncker J, Remue J, et al. One MRI-compatible tDCS session attenuates ventromedial cortical perfusion when exposed to verbal criticism: The role of perceived criticism. *Human Brain Mapping*. 2018;39(11):4462-4470. doi:10.1002/hbm.24285

139. Bogdanov M, Schwabe L. Transcranial Stimulation of the Dorsolateral Prefrontal Cortex Prevents Stress-Induced Working Memory Deficits. *Journal of Neuroscience*. 2016;36(4):1429-1437. doi:10.1523/JNEUROSCI.3687-15.2016

140. Dedoncker J, Vanderhasselt MA, Remue J, et al. Prefrontal TDCS attenuates medial prefrontal connectivity upon being criticized in individuals scoring high on perceived criticism. *Brain Imaging and Behavior*. 2019;13(4):1060-1070. doi:10.1007/s11682-018-9927-8

141. Boggio PS, Zaghi S, Fregni F. Modulation of emotions associated with images of human pain using anodal transcranial direct current stimulation (tDCS). *Neuropsychologia*. 2009;47(1):212-217. doi:10.1016/j.neuropsychologia.2008.07.022

142. Peña-Gómez C, Vidal-Piñeiro D, Clemente IC, Pascual-Leone Á, Bartrés-Faz D. Down-regulation of negative emotional processing by transcranial direct current stimulation: effects of personality characteristics. Aleman A, ed. *PLoS One*. 2011;6(7):e22812. doi:10.1371/journal.pone.0022812

143. Maeoka H, Matsuo A, Hiyamizu M, Morioka S, Ando H. Influence of transcranial direct current stimulation of the dorsolateral prefrontal cortex on pain related emotions: A study using electroencephalographic power spectrum analysis. *Neuroscience Letters*. 2012;512(1):12-16. doi:10.1016/j.neulet.2012.01.037

144. Rêgo GG, Lapenta OM, Marques LM, et al. Hemispheric dorsolateral prefrontal cortex lateralization in the regulation of empathy for pain. *Neurosci Lett*. 2015;594:12-16. doi:10.1016/j.neulet.2015.03.042

145. Carnevali L, Pattini E, Sgoifo A, Ottaviani C. Effects of prefrontal transcranial direct current stimulation on autonomic and neuroendocrine responses to psychosocial stress in healthy humans. *Stress*. Published online 2019:1-11. doi:10.1080/10253890.2019.1625884

146. Plewnia C, Schroeder PA, Kunze R, Faehling F, Wolkenstein L. Keep calm and carry on: improved frustration tolerance and processing speed by transcranial direct current stimulation (tDCS). Ward LM, ed. *PLoS One*. 2015;10(4):e0122578. doi:10.1371/journal.pone.0122578

147. Herrmann MJ, Simons BSE, Horst AK, Boehme S, Straube T, Polak T. Modulation of sustained fear by transcranial direct current stimulation (tDCS) of the right inferior frontal cortex (rIFC). *Biological Psychology*. 2018;139(July):173-177. doi:10.1016/j.biopsycho.2018.10.013

148. Riva P, Romero Lauro LJ, DeWall CN, Bushman BJ. Buffer the Pain Away. *Psychological Science*. 2012;23(12):1473-1475. doi:10.1177/0956797612450894

149. Vergallito A, Riva P, Pisoni A, Romero Lauro LJ. Modulation of negative emotions through anodal tDCS over the right ventrolateral prefrontal cortex. *Neuropsychologia*. 2018;119:128-135. doi:10.1016/j.neuropsychologia.2018.07.037

150. Koenigs M, Ukueberuwa D, Campion P, Grafman J, Wassermann E. Bilateral frontal transcranial direct current stimulation: Failure to replicate classic findings in healthy subjects. *Clinical Neurophysiology*. 2009;120(1):80-84. doi:10.1016/j.clinph.2008.10.010

151. Antal A, Fischer T, Saiote C, et al. Transcranial electrical stimulation modifies the neuronal response to psychosocial stress exposure. *Human Brain Mapping*. 2014;35(8):3750-3759. doi:10.1002/hbm.22434

152. Abend R, Sar-el R, Gonen T, et al. Modulating Emotional Experience Using Electrical Stimulation of the Medial-Prefrontal Cortex: A Preliminary tDCS-fMRI Study. *Neuromodulation: Technology at the Neural Interface*. http://doi.wiley.com/10.1111/ner.12787. Published May 9, 2018.

153. He Z, Lin Y, Xia L, Liu Z, Zhang D, Elliott R. Critical role of the right VLPFC in emotional regulation of social exclusion: A tDCS study. *Social Cognitive and Affective Neuroscience*. 2018;13(4):357-366. doi:10.1093/scan/nsy026

154. Feeser M, Prehn K, Kazzer P, Mungee A, Bajbouj M. Transcranial Direct Current Stimulation Enhances Cognitive Control During Emotion Regulation. *Brain Stimulation*. 2014;7(1):105-112. doi:10.1016/j.brs.2013.08.006

155. Marques LM, Morello LYN, Boggio PS. Ventrolateral but not Dorsolateral Prefrontal Cortex tDCS effectively impact emotion reappraisal – effects on Emotional Experience and Interbeat Interval. *Scientific Reports*. 2018;8(1):15295. doi:10.1038/s41598-018-33711-5

156. Chen NTM, Basanovic J, Notebaert L, MacLeod C, Clarke PJF. Attentional bias mediates the effect of neurostimulation on emotional vulnerability. *Journal of Psychiatric Research*. 2017;93:12-19. doi:10.1016/j.jpsychires.2017.05.008

157. Dittert N, Hüttner S, Polak T, Herrmann MJ. Augmentation of Fear Extinction by Transcranial Direct Current Stimulation (tDCS). *Frontiers in Behavioral Neuroscience*. 2018;12:76. doi:10.3389/fnbeh.2018.00076

158. Abend R, Jalon I, Gurevitch G, et al. Modulation of fear extinction processes using transcranial electrical stimulation. *Translational Psychiatry*. 2016;6(10):e913. doi:10.1038/tp.2016.197

159. Hortensius R, Schutter DJLG, Harmon-Jones E. When anger leads to aggression: induction of relative left frontal cortical activity with transcranial direct current stimulation increases the anger–aggression relationship. *Social Cognitive and Affective Neuroscience*. 2012;7(3):342-347. doi:10.1093/scan/nsr012

160. Kelley NJ, Eastwick PW, Harmon-Jones E, Schmeichel BJ. Jealousy increased by induced relative left frontal cortical activity. *Emotion*. 2015;15(5):550-555. doi:10.1037/emo0000068

161. Ganho-Ávila A, Gonçalves ÓF, Guiomar R, et al. The effect of cathodal tDCS on fear extinction: A cross-measures study. Schwenkreis P, ed. *PLOS ONE*. 2019;14(9):e0221282. doi:10.1371/journal.pone.0221282

162. Riva P, Romero Lauro LJ, Vergallito A, DeWall CN, Bushman BJ. Electrified emotions: Modulatory effects of transcranial direct stimulation on negative emotional reactions to social exclusion. *Soc Neurosci*. 2015;10(1):46-54. doi:10.1080/17470919.2014.946621

163. Downar J, Blumberger DM, Daskalakis ZJ. The Neural Crossroads of Psychiatric Illness: An Emerging Target for Brain Stimulation. *Trends in Cognitive Sciences*. 2016;20(2):107-120. doi:10.1016/j.tics.2015.10.007

164. Lantrip C, Gunning FM, Flashman L, Roth RM, Holtzheimer PE. Effects of transcranial magnetic stimulation on the cognitive control of emotion: Potential antidepressant mechanisms. *Journal of ECT*. 2017;33(2):73-80. doi:10.1097/YCT.0000000000000386

165. Schmeichel BJ, Volokhov RN, Demaree HA. Working Memory Capacity and the Self-Regulation of Emotional Expression and Experience. *Journal of Personality and Social Psychology*. 2008;95(6):1526-1540. doi:10.1037/a0013345

166. Valero-Cabré A, Amengual JL, Stengel C, Pascual-Leone A, Coubard OA. Transcranial magnetic stimulation in basic and clinical neuroscience: A comprehensive review of fundamental principles and novel insights. *Neuroscience & Biobehavioral Reviews*. 2017;83:381-404. doi:10.1016/j.neubiorev.2017.10.006

167. Priori A, Hallett M, Rothwell JC. Repetitive transcranial magnetic stimulation or transcranial direct current stimulation? *Brain Stimulation*. 2009;2(4):241-245. doi:10.1016/j.brs.2009.02.004

168. Lafon B, Rahman A, Bikson M, Parra LC. Direct Current Stimulation Alters Neuronal Input/Output Function. *Brain Stimulation*. 2017;10(1):36-45. doi:10.1016/j.brs.2016.08.014

169. Jacobson L, Koslowsky M, Lavidor M. tDCS polarity effects in motor and cognitive domains: a meta-analytical review. *Experimental Brain Research*. 2012;216(1):1-10. doi:10.1007/s00221-011-2891-9

170. Mosayebi Samani M, Agboada D, Jamil A, Kuo MF, Nitsche MA. Titrating the neuroplastic effects of cathodal transcranial direct current stimulation (tDCS) over the primary motor cortex. *Cortex*. 2019;119:350-361. doi:10.1016/J.CORTEX.2019.04.016

171. Schutter DJ, van Honk J, d'Alfonso AA, Postma A, de Haan EH. Effects of slow rTMS at the right dorsolateral prefrontal cortex on EEG asymmetry and mood. *Neuroreport*. 2001;12(3):445-447.

172. Jansen JM, Schluter RS, Goudriaan AE, van Holst RJ, van den Brink W. Differential Effects of Left and Right Prefrontal High-Frequency Repetitive Transcranial Magnetic Stimulation on Resting-State Functional Magnetic Resonance Imaging in Healthy Individuals. *Brain Connectivity*. 2017;8(2):60-67. doi:10.1089/brain.2017.0542

173. Harmon-Jones E, Gable PA. On the role of asymmetric frontal cortical activity in approach and withdrawal motivation: An updated review of the evidence. *Psychophysiology*. 2018;55(1):e12879. doi:10.1111/psyp.12879

174. Berkman ET, Kahn LE, Merchant JS. Training-Induced Changes in Inhibitory Control Network Activity. *The Journal of Neuroscience*. 2014;34(1):149-157. doi:10.1523/JNEUROSCI.3564-13.2014

175. Davidson RJ. Anterior cerebral asymmetry and the nature of emotion. *Brain and Cognition*. 1992;20(1):125-151. doi:10.1016/0278-2626(92)90065-T

176. Goodman RN, Rietschel JC, Lo LC, Costanzo ME, Hatfield BD. Stress, emotion regulation and cognitive performance: The predictive contributions of trait and state relative frontal EEG alpha asymmetry. *International Journal of Psychophysiology*. 2013;87(2):115-123. doi:10.1016/j.ijpsycho.2012.09.008

177. Wheeler RE, Davidson RJ, Tomarken AJ. Frontal brain asymmetry and emotional reactivity: A biological substrate of affective style. *Psychophysiology*. 2007;30(1):82-89. doi:10.1111/j.1469-8986.1993.tb03207.x

178. Koslov K, Mendes WB, Pajtas PE, Pizzagalli DA. Asymmetry in Resting Intracortical Activity as a Buffer to Social Threat. *Psychological Science*. 2011;22(5):641-649. doi:10.1177/0956797611403156

179. Zhang X, Bachmann P, Schilling TM, Naumann E, Schächinger H, Larra MF. Emotional stress regulation: The role of relative frontal alpha asymmetry in shaping the stress response. *Biological Psychology*. 2018;138:231-239. doi:10.1016/j.biopsycho.2018.08.007

180. Quaedflieg CWEM, Meyer T, Smulders FTY, Smeets T. The functional role of individual-alpha based frontal asymmetry in stress responding. *Biological Psychology*. 2015;104:75-81. doi:10.1016/j.biopsycho.2014.11.014

181. Sullivan RM, Gratton A. Prefrontal cortical regulation of hypothalamic–pituitary–adrenal function in the rat and implications for psychopathology: side matters. *Psychoneuroendocrinology*. 2002;27(1-2):99-114. doi:10.1016/S0306-4530(01)00038-5

182. Thibodeau R, Jorgensen RS, Kim S. Depression, anxiety, and resting frontal EEG asymmetry: A meta-analytic review. *Journal of Abnormal Psychology*. 2006;115(4):715-729. doi:10.1037/0021-843X.115.4.715

183. Eidelman-Rothman M, Levy J, Feldman R. Alpha oscillations and their impairment in affective and post-traumatic stress disorders. *Neuroscience and Biobehavioral Reviews*. 2016;68:794-815. doi:10.1016/j.neubiorev.2016.07.005

184. Carletti F, Fusar-Poli P, Abbamonte M, et al. Laterality effect on emotional faces processing: ALE meta-analysis of evidence. *Neuroscience Letters*. 2009;452(3):262-267. doi:10.1016/j.neulet.2009.01.065

185. Meyer T, Quaedflieg CWEM, Weijland K, Schruers K, Merckelbach H, Smeets T. Frontal EEG asymmetry during symptom provocation predicts subjective responses to intrusions in survivors with and without PTSD. *Psychophysiology*. 2018;55(1):e12779. doi:10.1111/psyp.12779

186. Hofman D, Schutter DJLG. Asymmetrical frontal resting-state beta oscillations predict trait aggressive tendencies and behavioral inhibition. *Social Cognitive and Affective Neuroscience*. 2012;7(7):850-857. doi:10.1093/scan/nsr060

187. Verona E, Sadeh N, Curtin JJ. Stress-induced asymmetric frontal brain activity and aggression risk. *Journal of Abnormal Psychology*. 2009;118(1):131-145. doi:10.1037/a0014376

188. Lea RG, Davis SK, Mahoney B, Qualter P. Does Emotional Intelligence Buffer the Effects of Acute Stress? A Systematic Review. *Frontiers in Psychology*. 2019;10:810. doi:10.3389/fpsyg.2019.00810

189. Hancock PA, Ross JM, Szalma JL. A Meta-Analysis of Performance Response Under Thermal Stressors. *Human Factors: The Journal of the Human Factors and Ergonomics Society*. 2007;49(5):851-877. doi:10.1518/001872007x230226

190. Bali A, Jaggi AS. Clinical experimental stress studies: methods and assessment. *Reviews in the Neurosciences*. 2015;26(5). doi:10.1515/revneuro-2015-0004

191. Chiesa A, Serretti A. Mindfulness-Based Stress Reduction for Stress Management in Healthy People: A Review and Meta-Analysis. *The Journal of Alternative and Complementary Medicine*. 2009;15(5):593-600. doi:10.1089/acm.2008.0495

192. Steinhardt M, Dolbier C. Evaluation of a resilience intervention to enhance coping strategies and protective factors and decrease symptomatology. *Journal of American College Health*. 2008;56(4):445-453. doi:10.3200/JACH.56.44.445-454

193. Galatzer-Levy IR, Brown AD, Henn-Haase C, Metzler TJ, Neylan TC, Marmar CR. Positive and negative emotion prospectively predict trajectories of resilience and distress among high-exposure police officers. *Emotion*. 2013;13(3):545-553. doi:10.1037/a0031314

194. Arnsten AFT. Stress signalling pathways that impair prefrontal cortex structure and function. *Nature Reviews Neuroscience*. 2009;10(6):410-422. doi:10.1038/nrn2648

195. Fisher PA, Beauchamp KG, Roos L, Noll LK, Flannery J, Delker B. The Neurobiology of Intervention and Prevention in Early Adversity. *Ssrn*. 2016;12(1):331-357. doi:10.1146/annurev-clinpsy-032814-112855

196. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. 2nd editio. Routledge; 1988. doi:10.4324/9780203771587

197. Benwell CSY, Learmonth G, Miniussi C, Harvey M, Thut G. Non-linear effects of transcranial direct current stimulation as a function of individual baseline performance: Evidence from biparietal tDCS influence on lateralized attention bias. *Cortex*. 2015;69:152-165. doi:10.1016/j.cortex.2015.05.007

198. McConathey EM, White NC, Gervits F, et al. Baseline Performance Predicts tDCS-Mediated Improvements in Language Symptoms in Primary Progressive Aphasia. *Frontiers in Human Neuroscience*. 2017;11:347. doi:10.3389/fnhum.2017.00347

199. Furuya S, Klaus M, Nitsche MA, Paulus W, Altenmüller E. Ceiling Effects Prevent Further Improvement of Transcranial Stimulation in Skilled Musicians. *The Journal of Neuroscience*. 2014;34(41):13834-13839. doi:10.1523/JNEUROSCI.1170-14.2014

200. Mottaghy FM, Pascual-Leone A, Kemna LJ, et al. Modulation of a brain–behavior relationship in verbal working memory by rTMS. *Cognitive Brain Research*. 2003;15(3):241-249. doi:10.1016/S0926-6410(02)00196-9

201. Antal A, Terney D, Poreisz C, Paulus W. Towards unravelling task-related modulations of neuroplastic changes induced in the human motor cortex. *European Journal of Neuroscience*. 2007;26(9):2687-2691. doi:10.1111/j.1460-9568.2007.05896.x

202. Fertonani A, Brambilla M, Cotelli M, Miniussi C. The timing of cognitive plasticity in physiological aging: a tDCS study of naming. *Frontiers in Aging Neuroscience*. 2014;6(JUN):131. doi:10.3389/fnagi.2014.00131

203. Hurley R, Machado L. Using transcranial direct current stimulation to improve verbal working memory: A detailed review of the methodology. *Journal of Clinical and Experimental Neuropsychology*. Published online 2018. doi:10.1080/13803395.2018.1434133

204. Bergmann TO, Karabanov A, Hartwigsen G, Thielscher A, Siebner HR. Combining non-invasive transcranial brain stimulation with neuroimaging and electrophysiology: Current approaches and future perspectives. *Neuroimage*. 2016;140:4-19. doi:10.1016/j.neuroimage.2016.02.012

205. Pell GS, Roth Y, Zangen A. Modulation of cortical excitability induced by repetitive transcranial magnetic stimulation: Influence of timing and geometrical parameters and underlying mechanisms. *Progress in Neurobiology*. 2011;93(1):59-98. doi:10.1016/j.pneurobio.2010.10.003

206. Monte-Silva K, Kuo MF, Hessenthaler S, et al. Induction of Late LTP-Like Plasticity in the Human Motor Cortex by Repeated Non-Invasive Brain Stimulation. *Brain Stimulation*. 2013;6(3):424-432. doi:10.1016/j.brs.2012.04.011

207. Maeda F, Keenan JP, Tormos JM, Topka H, Pascual-Leone A. Modulation of corticospinal excitability by repetitive transcranial magnetic stimulation. *Clinical Neurophysiology*. 2000;111(5):800-805. doi:10.1016/S1388-2457(99)00323-5

208. Bäumer T, Lange R, Liepert J, et al. Repeated premotor rTMS leads to cumulative plastic changes of motor cortex excitability in humans. *Neuroimage*. 2003;20(1):550-560. doi:10.1016/S1053-8119(03)00310-0

209. Hill AT, Fitzgerald PB, Hoy KE. Effects of Anodal Transcranial Direct Current Stimulation on Working Memory: A Systematic Review and Meta-Analysis of Findings From Healthy and Neuropsychiatric Populations. *Brain Stimulation*. 2016;9(2):197-208. doi:10.1016/j.brs.2015.10.006

210. Elmasry J, Loo C, Martin D. A systematic review of transcranial electrical stimulation combined with cognitive training. *Restorative Neurology and Neuroscience*. 2015;33(3):263-278. doi:10.3233/RNN-140473

211. McClintock SM, Reti IM, Carpenter LL, et al. Consensus Recommendations for the Clinical Application of Repetitive Transcranial Magnetic Stimulation (rTMS) in the Treatment of Depression. *The Journal of Clinical Psychiatry*. 2018;79(1):35-48. doi:10.4088/JCP.16cs10905

212. Pisoni A, Mattavelli G, Papagno C, Rosanova M, Casali AG, Romero Lauro LJ. Cognitive Enhancement Induced by Anodal tDCS Drives Circuit-Specific Cortical Plasticity. *Cerebral Cortex*. 2018;28(4):1132-1140. doi:10.1093/cercor/bhx021

213. Martin DM, Liu R, Alonzo A, Green M, Loo CK. Use of transcranial direct current stimulation (tDCS) to enhance cognitive training: effect of timing of stimulation. *Exp Brain Res*. 2014;232(10):3345-3351. doi:10.1007/s00221-014-4022-x

214. Gill J, Shah-basak PP, Hamilton R. It's the Thought That Counts: Examining the Task-dependent Effects of Transcranial Direct Current Stimulation on Executive Function. *Brain Stimulation*. 2015;8:253-259. doi:10.1016/j.brs.2014.10.018

215. Mancuso LE, Ilieva IP, Hamilton RH, Farah MJ. Does Transcranial Direct Current Stimulation Improve Healthy Working Memory?: A Meta-analytic Review. *Journal of Cognitive Neuroscience*. 2016;28(8):1063-1089. doi:10.1162/jocn_a_00956

216. Simonsmeier BA, Grabner RH, Hein J, Krenz U, Schneider M. Electrical brain stimulation (tES) improves learning more than performance: A meta-analysis. *Neuroscience & Biobehavioral Reviews*. 2018;84:171-181. doi:10.1016/j.neubiorev.2017.11.001

217. Kronberg G, Bridi M, Abel T, Bikson M, Parra LC. Direct Current Stimulation Modulates LTP and LTD: Activity Dependence and Dendritic Effects. *Brain Stimulation*. 2017;10(1):51-58. doi:10.1016/j.brs.2016.10.001

218. Heeren A, Baeken C, Vanderhasselt MA, Philippot P, de Raedt R. Impact of Anodal and Cathodal Transcranial Direct Current Stimulation over the Left Dorsolateral Prefrontal Cortex during Attention Bias Modification: An Eye-Tracking Study. Hills PJ, ed. *PLOS ONE*. 2015;10(4):e0124182. doi:10.1371/journal.pone.0124182

219. Clarke PJFF, Browning M, Hammond G, Notebaert L, Macleod C. The Causal Role of the Dorsolateral Prefrontal Cortex in the Modification of Attentional Bias: Evidence from Transcranial Direct Current Stimulation. *Biol Psychiatry*. Published online 2014:1-7. doi:10.1016/j.biopsych.2014.03.003

220. Martin DM, Liu R, Alonzo A, et al. Can transcranial direct current stimulation enhance outcomes from cognitive training? A randomized controlled trial in healthy participants. *The International Journal of Neuropsychopharmacology*. 2013;16(09):1927-1936. doi:10.1017/S1461145713000539

221. Berryhill ME, Martin D. Cognitive Effects of Transcranial Direct Current Stimulation in Healthy and Clinical Populations: An Overview. *Journal of ECT*. 2018;34(3):e25-e35. doi:10.1097/YCT.0000000000000534

222. Bajbouj M, Padberg F. A perfect match: noninvasive brain stimulation and psychotherapy. *European Archives of Psychiatry and Clinical Neuroscience*. 2014;264(S1):27-33. doi:10.1007/s00406-014-0540-6

223. Segrave RA, Arnold S, Hoy K, Fitzgerald PB. Concurrent Cognitive Control Training Augments the Antidepressant Efficacy of tDCS: A Pilot Study. *Brain Stimulation*. 2014;7(2):325-331. doi:10.1016/j.brs.2013.12.008

224. Li CT, Hsieh JC, Huang HH, et al. Cognition-Modulated Frontal Activity in Prediction and Augmentation of Antidepressant Efficacy: A Randomized Controlled Pilot Study. *Cerebral Cortex*. 2016;26(1):202-210. doi:10.1093/cercor/bhu191

225. Chalah MA, Ayache SS. Noninvasive Brain Stimulation and Psychotherapy in Anxiety and Depressive Disorders: A Viewpoint. *Brain Sciences*. 2019;9(4):82. doi:10.3390/brainsci9040082

226. Martin DM, McClintock SM, Forster JJ, Lo TY, Loo CK. Cognitive enhancing effects of rTMS administered to the prefrontal cortex in patients with depression: A systematic review and meta-analysis of individual task effects. *Depression and Anxiety.* 2017;34(11):1029-1039. doi:10.1002/da.22658

227. Martin DM, McClintock SM, Forster J, Loo CK. Does Therapeutic Repetitive Transcranial Magnetic Stimulation Cause Cognitive Enhancing Effects in Patients with Neuropsychiatric Conditions? A Systematic Review and Meta-Analysis of Randomised Controlled Trials. *Neuropsychology Review*. 2016;26(3):295-309. doi:10.1007/s11065-016-9325-1

228. Isserles M, Shalev AY, Roth Y, et al. Effectiveness of deep transcranial magnetic stimulation combined with a brief exposure procedure in post-traumatic stress disorder-a pilot study. *Brain Stimulation*. 2013;6(3):377-383. doi:10.1016/j.brs.2012.07.008

229. Osuch EA, Benson BE, Luckenbaugh DA, Geraci M, Post RM, McCann U. Repetitive TMS combined with exposure therapy for PTSD: a preliminary study. *J Anxiety Disord*. 2009;23(1):54-59. doi:10.1016/j.janxdis.2008.03.015

230. Asthana M, Nueckel K, Mühlberger A, et al. Effects of transcranial direct current stimulation on consolidation of fear memory. *Front Psychiatry*. 2013;4:107. doi:10.3389/fpsyt.2013.00107

231. van 't Wout M, Mariano TY, Garnaat SL, Reddy MK, Rasmussen SA, Greenberg BD. Can Transcranial Direct Current Stimulation Augment Extinction of Conditioned Fear? *Brain Stimulation*. 2016;9(4):529-536. doi:10.1016/j.brs.2016.03.004

232. Mungee A, Kazzer P, Feeser M, Nitsche MA, Schiller D, Bajbouj M. Transcranial direct current stimulation of the prefrontal cortex: a means to modulate fear memories. *Neuroreport*. 2014;25(7):480-484. doi:10.1097/WNR.0000000000000119

233. Mungee A, Burger M, Bajbouj M. No Effect of Cathodal Transcranial Direct Current Stimulation on Fear Memory in Healthy Human Subjects. *Brain Sci.* 2016;6(4). doi:10.3390/brainsci6040055

234. Notzon S, Deppermann S, Fallgatter A, et al. Psychophysiological effects of an iTBS modulated virtual reality challenge including participants with spider phobia. *Biological Psychology*. 2015;112:66-76. doi:10.1016/j.biopsycho.2015.10.003

235. Faehling F, Plewnia C. Controlling the Emotional Bias: Performance, Late Positive Potentials, and the Effect of Anodal Transcranial Direct Current Stimulation (tDCS). *Front Cell Neurosci.* 2016;10:159. doi:10.3389/fncel.2016.00159

236. Pripfl J, Neumann R, Köhler U, Lamm C. Effects of transcranial direct current stimulation on risky decision making are mediated by “hot” and “cold” decisions, personality, and hemisphere. *European Journal of Neuroscience*. Published online 2013. doi:10.1111/ejn.12375

237. Moreno ML, Vanderhasselt MA, Carvalho AF, et al. Effects of acute transcranial direct current stimulation in hot and cold working memory tasks in healthy and depressed subjects. *Neuroscience Letters*. 2015;591:126-131. doi:10.1016/j.neulet.2015.02.036

238. Herrmann MJ, Beier JS, Simons B, Polak T. Transcranial Direct Current Stimulation (tDCS) of the Right Inferior Frontal Gyrus Attenuates Skin Conductance Responses to Unpredictable Threat Conditions. *Frontiers in Human Neuroscience*. 2016;10(July):1-6. doi:10.3389/fnhum.2016.00352

239. Remue J, Vanderhasselt MA, Baeken C, Rossi V, Tullo J, De Raedt R. The effect of a single HF-rTMS session over the left DLPFC on the physiological stress response as measured by heart rate variability. *Neuropsychology*. 2016;30(6):756-766. doi:10.1037/neu0000255

240. Schroeder PA, Ehlis AC, Wolkenstein L, Fallgatter AJ, Plewnia C. Emotional Distraction and Bodily Reaction: Modulation of Autonomous Responses by Anodal tDCS to the Prefrontal Cortex. *Frontiers in Cellular Neuroscience*. 2015;9:482. doi:10.3389/fncel.2015.00482

241. Barrett LF, Bliss-Moreau E, Quigley KS, Aronson KR. Interoceptive sensitivity and self-reports of emotional experience. *Journal of Personality and Social Psychology*. 2004;87(5):684-697. doi:10.1037/0022-3514.87.5.684

242. Dunn BD, Galton HC, Morgan R, et al. Listening to your heart: How interoception shapes emotion experience and intuitive decision making. *Psychological Science*. Published online 2010. doi:10.1177/0956797610389191

243. Barrett LF. Feelings or words? Understanding the content in self-report ratings of experienced emotion. *Journal of Personality and Social Psychology*. 2004;87(2):266-281. doi:10.1037/0022-3514.87.2.266

244. Austin EJ, Deary IJ, Gibson GJ, McGregor MJ, Dent JB. Individual response spread in self-report scales: Personality correlations and consequences. *Personality and Individual Differences*. 1998;24(3):421-438. doi:10.1016/S0191-8869(97)00175-X

245. Cowen AS, Keltner D. Self-report captures 27 distinct categories of emotion bridged by continuous gradients. *Proc Natl Acad Sci U S A*. Published online 2017. doi:10.1073/pnas.1702247114

246. Bradley MM, Lang PJ. Measuring emotion: The self-assessment manikin and the semantic differential. *Journal of Behavior Therapy and Experimental Psychiatry*. Published online 1994. doi:10.1016/0005-7916(94)90063-9

247. Hoffmann H, Scheck A, Schuster T, et al. Mapping discrete emotions into the dimensional space: An empirical approach. In: *Conference Proceedings - IEEE International Conference on Systems, Man and Cybernetics.* ; 2012. doi:10.1109/ICSMC.2012.6378303

248. Herbert C, Herbert BM, Pauli P. Emotional self-reference: Brain structures involved in the processing of words describing one’s own emotions. *Neuropsychologia*. Published online 2011. doi:10.1016/j.neuropsychologia.2011.06.026

249. Marin MF, Camprodon J a., Dougherty DD, Milad MR. Device-based brain stimulation to augment fear extinction: Implications for ptsd treatment and beyond. *Depression and Anxiety*. 2014;31(4):269-278. doi:10.1002/da.22252

250. Roth Y, Padberg F, Zangen A. Transcranial magnetic stimulation of deep brain regions: Principles and methods. In: *Advances in Biological Psychiatry*. Vol 23. KARGER; 2007:204-224. doi:10.1159/000101039

251. Zangen A, Roth Y, Voller B, Hallett M. Transcranial magnetic stimulation of deep brain regions: Evidence for efficacy of the H-Coil. *Clinical Neurophysiology*. 2005;116(4):775-779. doi:10.1016/j.clinph.2004.11.008

252. Janik AB, Rezlescu C, Banissy MJ. Enhancing Anger Perception With Transcranial Alternating Current Stimulation Induced Gamma Oscillations. *Brain Stimulation*. 2015;8(6):1138-1143. doi:10.1016/j.brs.2015.07.032

253. Schutter DJLG, van Honk J, Laman M, Vergouwen AC, Koerselman F. Increased sensitivity for angry faces in depressive disorder following 2 weeks of 2-Hz repetitive transcranial magnetic stimulation to the right parietal cortex. *The International Journal of Neuropsychopharmacology*. 2010;13(09):1155-1161. doi:10.1017/S1461145710000660

254. Schutter DJLG, Martin Laman D, van Honk J, Vergouwen AC, Koerselman GF. Partial clinical response to 2 weeks of 2 Hz repetitive transcranial magnetic stimulation to the right parietal cortex in depression. *The International Journal of Neuropsychopharmacology*. 2009;12(05):643. doi:10.1017/S1461145708009553

255. Ferrucci R, Giannicola G, Rosa M, et al. Cerebellum and processing of negative facial emotions: cerebellar transcranial DC stimulation specifically enhances the emotional recognition of facial anger and sadness. *Cogn Emot*. 2012;26(5):786-799. doi:10.1080/02699931.2011.619520

256. Schutter DJLG, van Honk J. The Cerebellum in Emotion Regulation: A Repetitive Transcranial Magnetic Stimulation Study. *The Cerebellum*. 2009;8(1):28-34. doi:10.1007/s12311-008-0056-6

257. Kohler CG, Hoffman LJ, Eastman LB, Healey K, Moberg PJ. Facial emotion perception in depression and bipolar disorder: A quantitative review. *Psychiatry Research*. 2011;188(3):303-309. doi:10.1016/j.psychres.2011.04.019

258. Paulus W. Transcranial electrical stimulation (tES - tDCS; tRNS, tACS) methods. *Neuropsychological Rehabilitation*. 2011;21(5):602-617. doi:10.1080/09602011.2011.557292

259. Schutter DJLG. Syncing your brain: electric currents to enhance cognition. *Trends in Cognitive Sciences*. 2014;18(7):331-333. doi:10.1016/j.tics.2014.02.011

260. Thut G, Bergmann TO, Fröhlich F, et al. Guiding transcranial brain stimulation by EEG/MEG to interact with ongoing brain activity and associated functions: A position paper. *Clinical Neurophysiology*. 2017;128(5):843-857. doi:10.1016/j.clinph.2017.01.003

261. Albouy P, Baillet S, Zatorre RJ. Driving working memory with frequency-tuned noninvasive brain stimulation. *Ann N Y Acad Sci*. 2018;1423(1):126-137. doi:10.1111/nyas.13664

262. Batsikadze G, Moliadze V, Paulus W, Kuo MF, Nitsche MA. Partially non-linear stimulation intensity-dependent effects of direct current stimulation on motor cortex excitability in humans. *The Journal of Physiology*. 2013;591(7):1987-2000. doi:10.1113/jphysiol.2012.249730

263. Hoy KE, Emonson MRL, Arnold SL, Thomson RH, Daskalakis ZJ, Fitzgerald PB. Testing the limits: Investigating the effect of tDCS dose on working memory enhancement in healthy controls. *Neuropsychologia*. 2013;51(9):1777-1784. doi:10.1016/j.neuropsychologia.2013.05.018

264. Jung SH, Shin JE, Jeong YS, Shin HI. Changes in motor cortical excitability induced by high-frequency repetitive transcranial magnetic stimulation of different stimulation durations. *Clinical Neurophysiology*. 2008;119(1):71-79. doi:10.1016/j.clinph.2007.09.124

265. Zaehle T, Sandmann P, Thorne JD, Jäncke L, Herrmann CS. Transcranial direct current stimulation of the prefrontal cortex modulates working memory performance: Combined behavioural and electrophysiological evidence. *BMC Neuroscience*. 2011;12(1):2. doi:10.1186/1471-2202-12-2

266. Lage C, Wiles K, Shergill SS, Tracy DK. A systematic review of the effects of low-frequency repetitive transcranial magnetic stimulation on cognition. *Journal of Neural Transmission*. 2016;123(12):1479-1490. doi:10.1007/s00702-016-1592-8

267. Jannati A, Block G, Oberman LM, Rotenberg A, Pascual-Leone A. Interindividual variability in response to continuous theta-burst stimulation in healthy adults. *Clinical Neurophysiology*. 2017;128(11):2268-2278. doi:10.1016/j.clinph.2017.08.023

268. Teo JTH, Bentley G, Lawrence P, et al. Late cortical plasticity in motor and auditory cortex: role of met-allele in BDNF Val66Met polymorphism. *The International Journal of Neuropsychopharmacology*. 2014;17(05):705-713. doi:10.1017/S1461145713001636

269. Cheeran B, Talelli P, Mori F, et al. A common polymorphism in the brain-derived neurotrophic factor gene (BDNF) modulates human cortical plasticity and the response to rTMS. *Journal of Physiology*. 2008;586(23):5717-5725. doi:10.1113/jphysiol.2008.159905

270. Ludwig H, Moliadze V, Thirugnanas-ambandam N, et al. Brain-derived neurotrophic factor (BDNF) gene polymorphisms shape cortical plasticity in humans. *Brain Stimulation*. 2010;3(4):230-237. doi:10.1016/j.brs.2009.12.003

271. Antonenko D, Nierhaus T, Meinzer M, et al. Age-dependent effects of brain stimulation on network centrality. *Neuroimage*. 2018;176:71-82. doi:10.1016/j.neuroimage.2018.04.038

272. Guse B, Falkai P, Wobrock T. Cognitive effects of high-frequency repetitive transcranial magnetic stimulation: a systematic review. *Journal of Neural Transmission*. 2010;117(1):105-122. doi:10.1007/s00702-009-0333-7

273. Ridding MC, Ziemann U. Determinants of the induction of cortical plasticity by non-invasive brain stimulation in healthy subjects. *The Journal of Physiology*. 2010;588(13):2291-2304. doi:10.1113/jphysiol.2010.190314

274. Huang YZ, Lu MK, Antal A, et al. Plasticity induced by non-invasive transcranial brain stimulation: A position paper. *Clinical Neurophysiology*. 2017;128(11):2318-2329. doi:10.1016/j.clinph.2017.09.007

275. Hsu TY, Juan CH, Tseng P. Individual Differences and State-Dependent Responses in Transcranial Direct Current Stimulation. *Frontiers in Human Neuroscience*. 2016;10:643. doi:10.3389/fnhum.2016.00643

276. Thielscher A, Antunes A, Saturnino GB. Field modeling for transcranial magnetic stimulation: A useful tool to understand the physiological effects of TMS? In: *2015 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society* (EMBC). IEEE; 2015:222-225. doi:10.1109/EMBC.2015.7318340

277. Fyer AJ, Dillon DJ, Gorman JM, Liebowitz MR, Klein DF. Measurement of lactate-induced panic and anxiety. *Psychiatry Research*. 2002;20(2):97-105. doi:10.1016/0165-1781(87)90002-3

278. Beam W, Borckardt JJ, Reeves ST, George MS. An efficient and accurate new method for locating the F3 position for prefrontal TMS applications. *Brain Stimulation*. 2009;2(1):50-54. doi:10.1016/j.brs.2008.09.006

279. Steyer R, Schwenkmezger P, Notz P, Eid M. Development of the Multidimensional Mood State Questionnaire (MDBF). Primary data. [Translated Title] (Version 1). Information ZPID. Trier: Center for Research Data in Psychology: PsychData of the Leibniz Institute for Psychology. Published online 2004. https://doi.org/10.5160/psychdata.srrf91en15

280. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. *J Pers Soc Psychol*. 1988;54(6):1063-1070. doi:10.1037/0022-3514.54.6.1063

281. McNair D, Maurice L, Droppleman L. Manual profile of mood states. Educational and Industrial Testing Service. Published online 1971

282. Argyle N, Deltito J, Allerup P, et al. The Panic-Associated Symptom Scale: measuring the severity of panic disorder. *Acta Psychiatrica Scandinavica*. 1991;83(1):20-26

283. Schaefer A, Nils F, Philippot P, Sanchez X. Assessing the effectiveness of a large database of emotion-eliciting films: A new tool for emotion researchers. *Cognition and Emotion.* 2010;24(7):1153-1172. doi:10.1080/02699930903274322

284. Lejuez CW, Kahler, Cristopher W, Brown RA. A Modified Computer Version of the Paced Auditory Serial Addtion Task (PASAT) as a Laboratory-Based Stressor. *The Behavioral Therapist*. Published online 2003

285. Spielberger CD, Gorsuch RL, Lushene PR, Vagg PR, Jacobs AG. *Manual for the State-Trait Anxiety Inventory.*; 1970

286. Kirschbaum C, Pirke KM, Hellhammer DH. The 'Trier Social Stress Test' – A Tool for Investigating Psychobiological Stress Responses in a Laboratory Setting. *Neuropsychobiology*. 1993;28(1-2):76-81. doi:https://doi.org/10.1159/000119004

APPENDIX: SEARCH TERMS

MEDLINE:

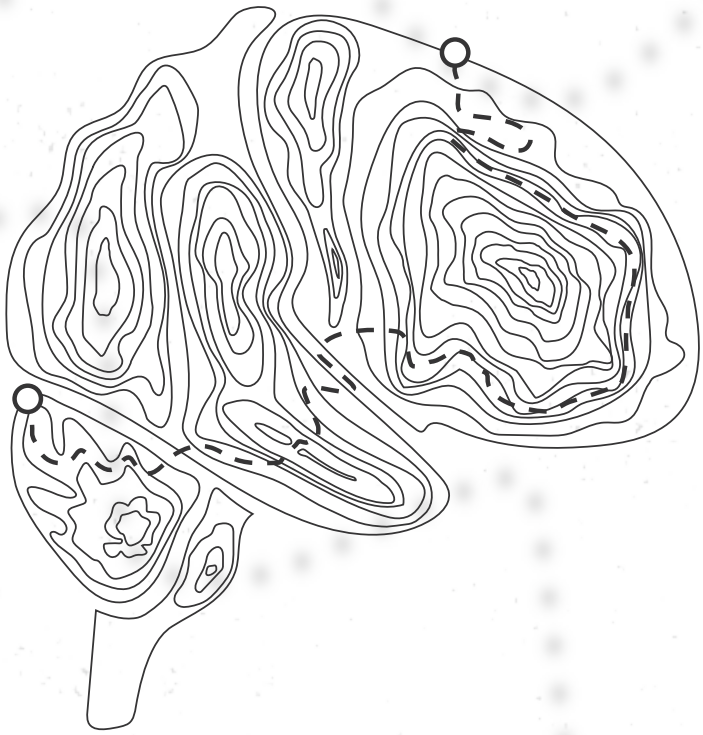
("noninvasive brain stimulation"[tw] OR "transcranial brain stimulation"[tw] OR "noninvasive cortical stimulation"[tw] OR "transcranial direct current stimulation"[tw] OR "repetitive transcranial magnetic stimulation"[tw] OR "theta burst stimulation"[tw] OR "transcranial electrical stimulation"[tw] OR "transcranial alternating current stimulation"[tw]) AND (stress[tw] OR stressor[tw] OR threat[tw] OR fear[tw] OR anxiety[tw] OR anxious[tw] OR emotion[tw] OR emotional[tw] OR aggression[tw] OR aggressive[tw]) AND (prefrontal[tw] OR frontal[tw] OR PFC[tw] OR *PFC) NOT "child"[MeSH Terms] NOT "infant"[MeSH Terms] AND ("Humans"[Mesh] OR human[tw] OR individuals[tw] OR participants[tw] OR subjects[tw] OR men[tw] OR women[tw]) NOT systematic[sb] NOT review[ptyp] NOT Case Reports[ptyp] AND English[lang] NOT "subthalamic nucleus"[tw] NOT "Deep Brain Stimulation"[Majr] NOT "oxidative stress"[tw]

WEB OF SCIENCE:

TS=("noninvasive brain stimulation" OR "transcranial brain stimulation" OR "noninvasive cortical stimulation" OR "transcranial direct current stimulation" OR "repetitive transcranial magnetic stimulation" OR "theta burst stimulation" OR "transcranial electrical stimulation") AND TS=(stress OR stressor OR threat OR fear OR anxiety OR anxious OR emotion OR emotional OR aggression OR aggressive) AND TS=(prefrontal OR frontal OR PFC OR *PFC) AND TS=(Humans OR human OR individuals OR participants OR subjects OR males OR men OR females OR women) NOT TS=(deep brain stimulation OR oxidative stress OR subthalamic nucleus OR review OR meta-analysis OR case report OR case series OR animal OR rat OR mouse OR child OR cranial)

SCOPUS:

(TITLE-ABS-KEY ("noninvasive brain stimulation" OR "transcranial brain stimulation" OR "noninvasive cortical stimulation" OR "transcranial direct current stimulation" OR "repetitive transcranial magnetic stimulation" OR "theta burst stimulation" OR "transcranial electrical stimulation")) AND (TITLE-ABS-KEY (humans OR individual OR participants OR subjects OR males OR men OR females OR women)) AND (TITLE-ABS-KEY (stress OR stressor OR threat OR fear OR anxiety OR anxious OR emotion OR emotional OR aggression OR aggressive)) AND (TITLE-ABS-KEY (prefrontal OR frontal OR pfc OR *pfc AND NOT "deep brain stimulation" OR "oxidative stress" OR "subthalamic nucleus" OR review OR meta-analysis OR "case report" OR "case series" OR animal OR rat OR mouse OR child OR cranial)) AND (LANGUAGE (english))



CHAPTER 3

Effects of tDCS during inhibitory control training on performance and PTSD, aggression and anxiety symptoms: A randomized controlled trial in a military sample

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ABSTRACT

Background: Posttraumatic stress disorder (PTSD), anxiety and impulsive aggression are linked to transdiagnostic neurocognitive deficits. This includes impaired inhibitory control over inappropriate responses. Prior studies showed that inhibitory control can be improved by modulating the right inferior frontal gyrus (IFG) with transcranial direct current stimulation (tDCS) in combination with inhibitory control training. However, its clinical potential remains unclear. We therefore aimed to replicate a tDCS-enhanced inhibitory control training in a clinical sample and test whether this reduces stress-related mental health symptoms.

Methods: In a preregistered double-blind randomized controlled trial, 100 active-duty military personnel and post-active veterans with PTSD, anxiety or impulsive aggression symptoms underwent a 5-session intervention where a stop-signal response inhibition training was combined with anodal tDCS over the right IFG for 20 minutes at 1.25 mA. Inhibitory control was evaluated with the emotional go/no-go task and implicit association test. Stress-related symptoms were assessed by self-report at baseline, post-intervention and after 3-months and 1-year follow-ups.

Results: Active relative to sham tDCS neither influenced performance during inhibitory control training nor on assessment tasks, and did also not significantly influence self-reported symptoms of PTSD, anxiety, impulsive aggression or depression at post-assessment or follow-up.

Conclusions: Our results do not support the idea that anodal tDCS over the right IFG at 1.25 mA enhances response inhibition training in a clinical sample, or that this tDCS-training combination can reduce stress-related symptoms. Applying different tDCS parameters or combining tDCS with more challenging tasks might provide better conditions to modulate cognitive functioning and stress-related symptoms.

INTRODUCTION

Posttraumatic stress disorder (PTSD) and anxiety are mental health disorders that are difficult to treat, particularly among military patients[1,2]. New treatment targets may be provided by findings ways to restore deficits in neurocognitive processes. Across patients with PTSD, anxiety, and impulsive aggression, dysregulated neurocognitive processes center around hyperresponsive limbic regions including the amygdala and (dorsal) anterior cingulate cortex (ACC)[3–5] and hyporesponsive regions in the lateral and medial prefrontal cortex (PFC), accompanied by impairments in cognitive functions like working memory, cognitive flexibility and inhibitory control[6].

Of these cognitive functions, inhibitory control particularly may play a vital role. Inhibitory control comprises the ability to withhold automatic or context-inappropriate responses in order to maintain goal-directed behavior. PTSD patients display impairments specifically on inhibitory control tasks[7] and hypoactivation in the brain's hub of inhibitory control: the right inferior frontal gyrus (IFG)[3,8]. It is proposed that failing inhibition of inappropriate stress responses, memories and motor reactions to fear-evoking stimuli contributes to symptoms of hyperarousal and irritability, and in turn, avoidance of fear- or trauma-related triggers and defensive aggression[9,10]. Moreover, impairments in the prefrontal inhibitory control circuit may impede therapy response[11]. An appealing question is therefore whether the dysregulated inhibitory control circuit poses a potential therapeutic target.

To restore dysregulated brain circuits, transcranial direct current stimulation (tDCS) may play a role by promoting neural plasticity[12]. While tDCS alone may not effectively modulate emotional distress[13], deficient cognitive processes underlying stress-related disorders – such as inhibitory control – could comprise convenient tDCS targets in this context. For example, single-session tDCS over the right IFG has shown to increase inhibitory control task performance[14,15]. Also with other techniques used to modulate right IFG functioning (e.g., transcranial magnetic stimulation, fMRI neurofeedback) inhibitory control can be enhanced[16,17]. Interestingly, multiple-session tDCS combined with response inhibition training has demonstrated cumulative effects on inhibitory control in healthy volunteers[18]. Increasing evidence now suggests that combining multiple tDCS sessions with cognitive training may produce stronger, more consistent and longer-lasting effects on and beyond the trained function[19]. Combining multiple-session tDCS with inhibitory control training may thus provide opportunities to target impairments in the prefrontal inhibitory control function. The next step in exploring the potential of tDCS-enhanced inhibitory control training in treating stress-related disorders is to replicate these effects in a clinical sample and test whether this beneficially affects clinically relevant outcomes.

In this randomized controlled trial (RCT), we applied a 5-session inhibitory control training with anodal tDCS over the right IFG in military veterans and active-duty personnel with PTSD, anxiety or impulsive aggression. As a primary outcome, we tested whether tDCS enhanced

inhibitory control during training. As secondary outcomes, we tested tDCS-related changes in inhibitory control performance and stress-related symptoms over the intervention period.

METHODS

This double-blind RCT was preregistered at the Netherlands Trial Register (www.trialregister.nl, ID: NL5709).

PARTICIPANTS

Military veterans and active-duty personnel of the Dutch Ministry of Defence were recruited between May 2016 and October 2019 through advertisements in mental healthcare outpatient clinics. The following inclusion criteria were applied: 18-60 years of age, fulfilling diagnostic criteria and receiving treatment for PTSD, an anxiety disorder or impulsive aggression problems. Exclusion criteria: primary diagnosis for major depressive disorder (comorbid depression was not a reason for exclusion), substance addiction, severe neurological or psychotic disorder, serious head trauma or surgery, large metal or ferromagnetic parts in the head, implanted pacemaker or neurostimulator, pregnancy, skin damage on the scalp, and neurostimulation in the past month. Psychoactive medication use was assessed. Patients were asked to keep stable doses during the tDCS intervention, starting two weeks in advance. The a priori computed sample size was 96 (48 per group; computed in G*Power 3.1[20] with $\alpha = 0.05$, $\beta = 90\%$, and Cohen's $f = 0.34$ based on results from Ditye and coworkers[18] lowered by 10%). The medical ethical committee of the University Medical Center Utrecht approved the study. All participants provided written informed consent. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

PROCEDURE AND RANDOMIZATION

Figure 1B depicts the study procedure. First, a clinical diagnostic interview was done, including the SCID-I for DSM-IV-R Axis-I disorders[21], DSM-5 intermittent explosive disorder criteria[22], and M.I.N.I. ADHD criteria[23]. Patients were then allocated to active or sham tDCS (1:1) by the next available stimulator-activating code from a randomized list (Matlab 'rand' function; 20 codes for active tDCS, 20 codes for sham), stratified by eye movement desensitization and reprocessing (EMDR) therapy vs. cognitive behavioral therapy (CBT) to avoid confounding with psychotherapy effects. Experimenters were blind for code-to-condition correspondence, and, although not formally tested, patients were not expected to know whether they received sham or active tDCS[24]. The interview and tDCS sessions were carried out in test rooms at the University Medical Center Utrecht. Pre- and post-assessments took place online through a weblink.

Table 1. Demographical and clinical participant characteristics.

		Active tDCS ***(n = 47)*** *mean (SD) or count*	**Sham** ***(n = 49)*** *mean (SD) or count*
Gender	Male: Female:	41 6	48 1
Age (years)[1]		40.5 (10.6)	44.4 (9.4)
Education level[2]	Low: Moderate: High:	4 30 13	1 30 18
Military status	Active-duty: Post-active veteran:	29 18	40 9
Number of deployments		2.6 (2.6)	3.3 (2.0)
Years since last deployment (years)		12.9 (11.3)	12.8 (10.0)
Treatment type during tDCS intervention[3]	EMDR: CBT: Other:	8 22 17	8 26 15
Use of psychoactive medication[4]	Yes: No:	18 29	15 34
Childhood trauma (based on CTQ-SF cut-off scores for moderate to extreme childhood trauma)	Yes: No:	30 17	30 18 *1 missing*
ADHD diagnosis	Yes: No:	7 40	6 43
Attentional impulsivity (BIS-11)		20.4 (3.5)	20.6 (3.5)
Motor impulsivity (BIS-11)		21.9 (3.6)	22.7 (3.4)
Non-planning impulsivity (BIS-11)		28.7 (4.4)	27.4 (4.7)
Diagnosis[5]:			
Impulsive aggression		23	22
Anxiety		16	24
PTSD		25	25

[1]Age was entered as a covariate in the statistical analyses. Excluding the *Age* covariate from the models did not significantly change the results.[2]Education level: Low = high school education only, Moderate = vocational degree, High = higher education degree.[3]EMDR = eye movement desensitization and reprocessing therapy, CBT = cognitive behavioral therapy.Other treatment included: aggression regulation training, mindfulness-based therapy, couples therapy, maintenance therapy by social workers, pharmacological treatment.[4]The majority of psychoactive drugs used in our sample comprised selective serotonin or serotonin-norepinephrine reuptake inhibitors (SSRI's and SNRI's), benzodiazepines, atypical antipsychotic drugs, norepinephrine-dopamine reuptake inhibitors (NDRI's) and anticonvulsants. Analysis of the primary outcome measure (SST training scores) showed similar results across medicated and unmedicated patients. Also, excluding *Use of psychoactive medication (yes/no)* as a covariate from the models did not significantly change the results of any other measure.[5]While most participants fulfilled criteria for either PTSD or anxiety or impulsive aggression, some participants fulfilled criteria for multiple stress-related diagnoses: PTSD and anxiety (n=10), PTSD and impulsive aggression (n=14), anxiety and impulsive aggression (n=6), or all three diagnoses (n=5).

TDCS

Participants received 5 tDCS sessions, with 1-5 days between sessions depending on the participant's availability. TDCS was applied for 20 minutes over two 5×7 cm electrodes by a neuroConn DC-stimulator Plus with settings based on Ditye's study[18]: 1.25 mA (fade-in: 8 s), anode on the crossing point between 10/20 EEG positions T4-Fz and F8-Cz, cathode over the left orbital region (see **Figure 1B**). Sham tDCS was applied by a 16-second fade-in fade-out stimulation at the start and end of the stimulation period, interleaved by occasional 15 ms pulses of 0.11 mA. Emotional state was assessed before and after each session by the STAI-6[25], together with possible tDCS side effects scored from 1 ("absent") to 4 ("severe")[26].

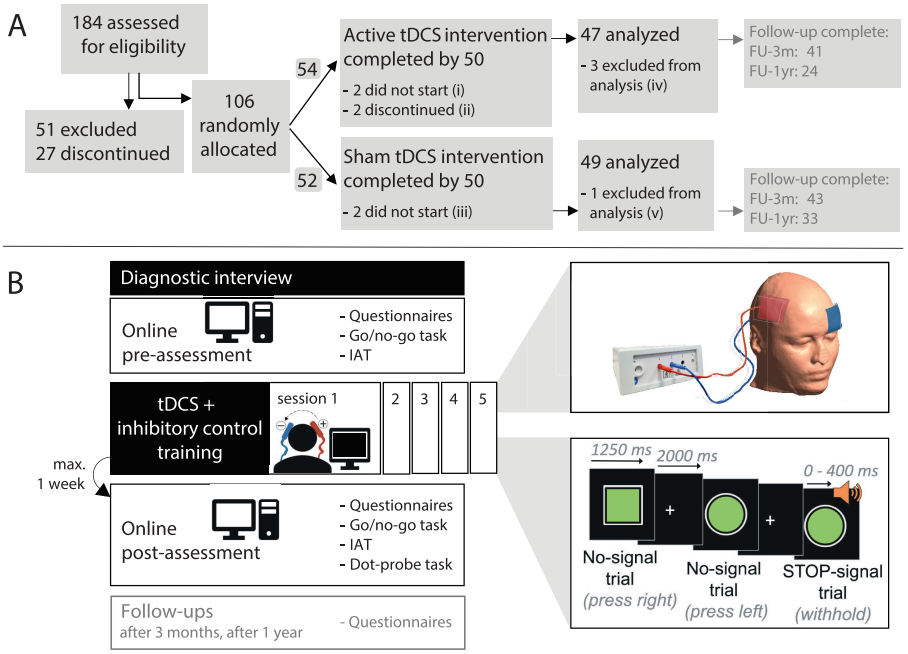

Figure 1. (A) CONSORT study flow diagram. FU-3m = 3-months follow-up assessment. FU-1yr = 1-year follow-up assessment. [i]Reasons: delayed discovery of tDCS safety contraindication (n=1), time conflict with other treatment/work (n=1). [ii]Reasons: panic symptoms at tDCS work-up session 1 (n=1), time conflict with other treatment (n=1). [iii]Reasons: time conflict with other treatment/work (n=2). [iv]Reasons: psychoactive drug changes during intervention (n=1), >5 days between tDCS sessions (n=1), tDCS applied at <1.25 mA on request of participant (n=1); [v]Reasons: inadequate performance of the stop-signal task (n=1); **(B)** Overview of study procedure.

INHIBITORY CONTROL TRAINING

TDCS was combined with a 30-minute training on the stop-signal task, see **Figure 1B**[27]. Participants were instructed to quickly press the left or right arrow button upon stimulus presentation (circle or square), but to withhold their response when a stop-signal was heard: an auditory "beep" (25% of trials, 0-400 ms stop-signal onset delay). To titrate successful

stop-signal response inhibition to ~50%, stop-signal delays increased or decreased with 50 ms after successful or unsuccessful stopping respectively. Six blocks of 100 trials were interleaved by 1-minute breaks. One extra block with 20 no-signal trials to prevent response slowing was excluded from data analysis. The stop-signal response time (SSRT), the time it takes to stop an already initiated response which reflects inhibitory control, was computed by the independent horse-race model[27] and constituted our primary outcome measure. Response speed (RT on no-signal trials) was taken as a control measure.

SECONDARY OUTCOME MEASURES OF INHIBITORY CONTROL

Prolonged effects of training combined with active vs. sham tDCS on inhibitory control were tested by comparing performance at pre- vs. post-assessment on the emotional go/no-go task and the implicit association task (IAT).

The go/no-go task was used to measure inhibition of prepotent responses driven by a high frequency of go-stimuli. Participants were instructed to rapidly tap on the space bar when a go-stimulus appeared (80% of trials), and to withhold their response to a no-go-stimulus (20% of trials). On 50% of all trials, 'go'- and 'no-go'-stimuli ('[]' and ']['') were superimposed on male face images with a neutral or angry expression (Bochum Emotional Stimulus Set, BESST[72]), to assess threat-related distraction on inhibition performance[29]. Stimuli were presented for 600 ms with a 250-350 ms inter-trial interval in 7 blocks of 40 trials. The median reaction time (RT) over go-trials was used to assess effects on response speed, and accuracy represented the ability to correctly execute or inhibit responses. The first (practice) block, the first 4 trials of each block, post-error trials, sequences of ≥ 5 consecutive no-response go-trials, and trials with an RT<170 ms were excluded from analysis (on average, 18.5% of trials were excluded).

The IAT was used to measure inhibition of prepotent responses driven by automatic associations. We used the standard IAT with flower and insect names as target words and pleasant and unpleasant words as attributes[30]. Participants were instructed to classify target and attribute words as quickly as possible by pressing the 'F' or 'J' button. Each category contained 15 practice trials and 60 test trials. Better inhibition of the automatic response attenuates the increase in response latency and error rate on incongruent trials (the IAT effect). The D600 IAT effect was computed by adding 600 ms to incorrect response RTs, and dividing the difference in congruent vs. incongruent trial RTs by the RT standard deviation. In addition, a Quad model[31] was estimated based on trial-level classification errors using a multinomial tree processing model in R[32], to quantify the "overcoming bias" (the likelihood that the automatic association is overcome), representing the unique contribution of inhibitory control on IAT performance.

At post-assessment, participants additionally performed a dot-probe task. Unlike the inhibitory control tasks, this task assesses attentional biases for threat. The main outcomes of this task are described in the Appendix.

SYMPTOMS

Beside baseline symptom assessment by the diagnostic interview, symptom levels were assessed at pre-, post- and follow-up-assessments by self-report scales including the PTSD Checklist for DSM-5 (PCL-5)[33], the trait version of the Positive and Negative Affect Schedule (PANAS)[34], and the STAXI-2[35]. TDCS effects on disorder-specific symptoms of PTSD, anxiety and impulsive aggression were tested only within subgroups of participants who fulfilled criteria for the corresponding diagnosis. Depressive symptoms and general mental wellbeing were assessed using the Beck Depression Inventory 2nd edition (BDI-II)[36] and the Outcome Questionnaire 45 (OQ45)[37]. At baseline, childhood trauma and impulsivity traits were assessed by the Dutch version of the childhood trauma questionnaire short form (CTQ-SF)[38] and the Barrett's Impulsivity Scale (BIS-11)[39].

STATISTICAL ANALYSIS

Continuous outcomes were analyzed in mixed design ANOVAs in R[40] with the "rstatix" package[41]. Trial-level accuracy data were, as recommended[42], analyzed in binary logistic mixed-effects models with the "lme4" package[43] with a random intercept for participant, where *p*-values were obtained in likelihood ratio tests of the full model vs. a model without the effect. *Stimulation group* (active vs. sham tDCS) was treated as between-subjects factor, *Time* (tDCS sessions 1-5, or pre-assessment, post-assessment and follow-ups) as within-subjects factor, and their interaction would reflect whether the active tDCS intervention induced different time effects than the sham intervention. *Age* and *Use of psychoactive medication* (yes/no) were included as covariates. Where the assumption of sphericity was violated, Greenhouse-Geisser-corrected results are reported. Effects are reported as significant at $p < .05$. Effect sizes are reported as generalized eta-squared (η^2_G).

Additionally, to provide possibly useful information for neurocognitive models about the relationship between inhibitory control and stress-related symptoms, we computed baseline correlations between the inhibitory control tasks and symptom scores at pre-assessment. Also, to explore if improved inhibitory control could drive symptom relief, we tested in a regression model if (i) SSRT improvement (ΔSSRT = SSRT session 5 – SSRT session 1) or (ii) the achieved SSRT level on session 5 predicted reductions in PTSD, anxiety or anger symptoms (Δsymptom score = post-score – pre-score). Here, *Stimulation group* was always entered as a first predictor to control for effects attributable to tDCS.

RESULTS

Figure 1A shows the study flow. As can be seen in **Table 1**, the active tDCS and sham groups matched on most factors. Yet, despite random group allocation, females and post-active veterans were overrepresented in the active tDCS group, while patients with an anxiety diagnosis were overrepresented in the sham group. Because prefrontal tDCS outcomes may depend on gender[44], we repeated analyses without the female participants, which did not significantly change results.

SAFETY

The intervention was well tolerated and no serious adverse events were reported. The only tDCS-related side effects were mild itching and burning sensations on the scalp (mean severity scores ±SD | itching – active tDCS: 1.7 ±0.7 vs. sham: 1.4 ±0.6; burning – active tDCS: 1.6 ±0.7 vs. sham: 1.3 ±0.6; *p*'s < .001), and some tDCS participants noticed light skin redness that was absent in the sham group (active tDCS: 1.1 ±0.6 vs. sham: 1.0 ±0.1; $p = .010$). Emotional state fluctuations during tDCS sessions were negligible and did not significantly differ between stimulation groups (mean STAI-6 item absolute change score: 0.26 ±0.48; effects of *Stimulation group* and *Stimulation group* × *STAI6- item* on change scores: *p*'s > 0.18).

PRIMARY OUTCOME: INHIBITORY CONTROL TRAINING ON THE STOP-SIGNAL TASK

Three participants showed very slow response times on session 1, preventing reliable SSRT computations. As this comprised <5% of the data, the a priori defined analyses were performed on the remaining sample (46 tDCS and 47 sham)[45]. A mean stop-signal response accuracy of 51.5% ±7% confirmed successful stop-signal delay titration.

The active vs. sham tDCS groups did not significantly differ in overall SSRT scores or in SSRT improvement over sessions, as indicated by the non-significant effects of *Stimulation group* and the *Stimulation group* × *Time* interaction (respectively: $p = .239$, $\eta^2_G = .011$; $p = .582$, $\eta^2_G = .002$). Only the main effect of *Time* was significant ($p < .001$, $\eta^2_G = .019$). SSRT changes between sessions were tested with post-hoc Bonferroni-corrected pairwise t-tests; the SSRT significantly decreased from session 1 to session 2 and all following sessions, from session 2 to session 3 and all following sessions, and from session 3 to session 5 (*p*'s < .01), see **Figure 2**. When *Diagnosis* was entered as an additional between-subjects factor to explore possible differences between patient subgroups, the tDCS related effects remained non-significant (*Stimulation group*: $p = .255$, $\eta^2_G = .011$; *Stimulation group* × *Time*: $p = .905$, $\eta^2_G < .001$; *Stimulation group* × *Time* × *Diagnosis*: $p = .201$, $\eta^2_G = .009$). However, beside a main effect of *Time* ($p < .001$, $\eta^2_G = .018$), a significant *Time* × *Diagnosis* interaction appeared ($p = .005$, $\eta^2_G = .020$). Based on visual inspection of the SSRTs per subgroup, the interaction seemed to reflect a relatively strong SSRT decrease in the PTSD subgroup compared to the anxiety and aggression subgroups (see **Figure S.2.** in the Appendix). Next, despite the underpowered 2 × 5 mixed design for the diagnosis subgroups, the subgroups were analyzed separately. The main effect of *Time* remained significant among PTSD patients ($p = .014$, $\eta^2_G = .028$), and was non-significant in the anxiety and aggression subgroups (respectively: $p = .094$, $\eta^2_G = .019$; $p = .083$, $\eta^2_G = .036$).

Concerning the no-signal RT, no significant effects of active vs. sham tDCS appeared either (*Stimulation group* main effect: $p = .338$, $\eta^2_G = .012$; *Stimulation group* × *Time* interaction: $p = .309$, $\eta^2_G = .003$), although participants did become faster over sessions (main effect of *Time*: $p < .001$, $\eta^2_G = .024$). For further details on the no-signal RT, see **Figure S.2.**

In an additional analysis, we explored if tDCS effects on inhibitory control training would depend on baseline levels of inhibitory control, which was assessed by the go/no-go task. To that end,

we regressed the total SSRT improvement from session 1 to 5 on the predictors *pre-assessment Go/no-go scores* (RT and accuracy) and *Stimulation group*. Results showed no evidence for a dependence of tDCS effects on baseline inhibitory control performance (*Stimulation group* × *Go/NoGo scores* interaction effects: *p*'s > .418). Analysis details can be found in the Appendix.

SECONDARY OUTCOMES OF INHIBITORY CONTROL

Means and standard deviations per group are reported in **Table 2**, together with the outcomes of the *Stimulation group* × *Time* interaction effects of interest.

Go/no-go task. Go/no-go data from 80 participants were available for analysis (40 tDCS, 40 sham; missings due to insufficient (<100) completed trials, n=5; post-assessment unavailable or completed >1 week after tDCS intervention, n=11). TDCS did not influence response speed or response inhibition accuracy: pre-to-post intervention changes in RT or no-go accuracy were not significantly different between active and sham tDCS groups (see **Table 2**). Response speed did not significantly change over time or differ between groups at all (main effect *Time*: $p = .273$, *Stimulation group*: $p = .374$). For accuracy, a significant *Go/no-go* × *Time* interaction ($p = .005$; $\beta = 0.41$, std. error = 0.15) and a significant *Stimulation group* × *Time* interaction appeared ($p = .008$; $\beta = -0.17$, std. error = 0.06). Bonferroni-corrected pairwise t-tests showed that go-trial accuracy increased from pre- to post-assessment in both stimulation groups (go-trials – pre vs. post: $p < .001$). Such effects were not found for no-go accuracy (i.e., response inhibition accuracy – pre vs. post: $p > .999$). Moreover, the stimulation groups differed in overall performance accuracy at post-assessment, where the sham group made significantly less errors than the active tDCS group (pre-assessment – active tDCS vs. sham: $p = 0.898$; post-assessment – active tDCS vs. sham: $p = .011$), suggesting a lack of improvement in overall performance accuracy over time in the active tDCS group. Again, no group differences were found specifically in no-go accuracy (response inhibition). Furthermore, the face distractors significantly impaired task performance: *Distractor condition* showed a significant main effect on both RT and accuracy (*p*'s < .001). Follow-up t-tests and χ^2 tests showed that RTs were faster on trials with face distractors (distractor vs. no-distractor: $p < .001$, neutral vs. angry distractor: $p = .690$). This distractor-induced RT acceleration also yielded a *Stimulation group* × *Distractor condition* interaction ($p = .047$), showing it was more pronounced in the active vs. sham tDCS group ($p = .034$). Error rates increased from no-distractor- to neutral face distractor- to angry face distractor-trials (*p*'s < .045).

IAT. IAT data from 84 participants were available for analysis (43 tDCS, 41 sham; missings due to post-assessment unavailable or completed >1 week after tDCS intervention, n=12). Pre-to-post intervention changes in the D600 IAT effect did not significantly differ between the active tDCS and sham group (see **Table 2**). The IAT effect significantly increased from pre- to post-assessment ($p = .042$, $\eta^2_G = .021$), indicating a possible reduction in inhibitory control over biases due to automatic associations. The Quad model "overcoming bias" parameter did not appear significantly affected by *Stimulation group*, but the overall model fit was very low, suggesting the Quad model results were not reliable (model fit for post-assessment IAT data – tDCS group: $G^2(6) = 11.33$, $p = .079$, AIC = 23.33; sham: group $G^2(6) = 13.00$, $p = .043$, AIC = 25.00). The full analysis is reported in the Appendix.

Table 2. Statistical outcomes.

tDCS					Sham			
Non-trained inhibitory control tasks (mean ±standard deviation)								
	Pre	**Post**			**Pre**	**Post**		
Go/no-go task – Go trial RT *(in ms)*								
No-distr.:	415 ±38	409 ±43			403 ±41	397 ±44		
Neutral:	392 ±37	391 ±42			391 ±43	384 ±44		
Angry:	395 ±35	392 ±42			389 ±41	387 ±47		
		Stimulation group × Time		*p* = .797	η^2_G = < .001			
		Stimulation group × Time × Distractor		*p* = .310	η^2_G = < .001			
Go/no-go task – total No-go trial error rate								
No-distr.:	0.38	0.37			0.42	0.35		
Neutral:	0.59	0.78			0.66	0.57		
Angry:	0.64	0.81			0.55	0.53		
		Stimulation group × Time × Go/no-go		*p* = .727	β (SE) = 0.17 (0.20)			
		Stimulation group × Time × Go/no-go × Distractor		*p* = .791	β (SE) = -0.02 (0.24)			
D600 IAT effect								
0.67 ±.38		0.84 ±.27			0.74 ±.30	0.77 ±.38		
		Stimulation group × Time		*p* = .140	η^2_G = .011			
Symptoms (mean item score ±standard deviation)								
Pre		**Post**	**FU3m**	**FU1yr**	**Pre**	**Post**	**FU3m**	**FU1yr**
PTSD symptoms (PCL-5)								
2.45 ±.55		2.02 ±.72	1.84 ±.83	1.55 ±.87	2.19 ±.63	2.07 ±.72	1.60 ±.77	1.46 ±.92
		n = 23	*n = 22*	*n = 13*		*n = 23*	*n = 21*	*n = 18*
	Pre-post:	*Stimulation group × Time*		*p* = .023	η^2_G = .010			
	incl. FU's:	*Stimulation group × Time*		*p* = .572	η^2_G = .004			
Anxiety symptoms (PANAS Negative Affect)								
2.70 ±.80		2.37 ±.88	2.15 ±.82	2.34 ±.49	2.90 ±.68	2.56 ±.72	2.36 ±.74	2.56 ±.75
		n = 15	*n = 14*	*n = 9*		*n = 22*	*n = 19*	*n = 16*
	Pre-post:	*Stimulation group × Time*		*p* = .843	< .001			
	incl. FU's:	*Stimulation group × Time*		*p* = .953	.001			
Aggression symptoms (STAXI-2 Trait Anger)								
2.60 ±.61		2.37 ±.58	2.13 ±.57	1.99 ±.51	2.28 ±.58	2.28 ±.64	2.08 ±.56	1.98 ±.56
		n = 22	*n = 20*	*n = 10*		*n =20*	*n = 17*	*n = 12*
	Pre-post:	*Stimulation group × Time*		*p* = .243	η^2_G = .005			
	incl. FU's:	*Stimulation group × Time*		*p* = .980	η^2_G < .001			
Depressive symptoms (BDI-II)								
1.93 ±.49		1.71 ±.51	1.65 ±.56	1.62 ±.48	2.03 ±.47	1.83 ±.49	1.69 ±.41	1.74 ±.57
		n = 44	*n = 40*	*n = 25*		*n = 46*	*n = 41*	*n = 33*
	Pre-post:	*Stimulation group × Time*		*p* = .885	η^2_G = < .001			
	incl. FU's:	*Stimulation group × Time*		*p* = .213	η^2_G = .007			

■ **Table 2.** (Continued)

tDCS				Sham			
Pre	**Post**	**FU3m**	**FU1yr**	**Pre**	**Post**	**FU3m**	**FU1yr**
***General wellbeing (OQ45)*[a]**							
SD: 1.70 ±.62	1.49 ±.65	1.49 ±.68	1.27 ±.60	1.76 ±.52	1.62 ±.51	1.49 ±.60	1.43 ±.68
IR: 1.42 ±.57	1.28 ±.59	1.29 ±.60	1.13 ±.57	1.57 ±.60	1.43 ±.62	1.34 ±.65	1.37 ±.66
SR: 1.63 ±.60	1.49 ±.56	1.43 ±.56	1.37 ±.51	1.43 ±.56	1.35 ±.53	1.27 ±.39	1.28 ±.46
AA: 1.75 ±.70	1.50 ±.72	1.58 ±.72	1.34 ±.68	1.77 ±.53	1.62 ±.51	1.48 ±.59	1.41 ±.68
	n = 44	*n = 41*	*n = 25*		*n = 45*	*n = 41*	*n = 31*
Pre-post: *Stimulation group × Subscale × Time*			*p* = .266	η^2_G < .001			
incl. FU's: *Stimulation group × Subscale × Time*			*p* = .374	η^2_G = .001			

FU3m = 3-months follow-up assessment. FU1yr = 1-year follow-up assessment.
[a]: SD = Symptom Distress, IR = Interpersonal Relations, SR = Social Role, AA = Anxious Arousal.

SYMPTOMS

The analysis of PTSD symptoms was only carried out within the subgroup of PTSD patients, the analysis on anxiety symptoms only within the subgroup of anxiety patients, and likewise for the impulsive aggression patients. Data were available for analysis per diagnosis subgroup as indicated in **Table 2** (missings due to unavailable post-assessment or completed >1 week after tDCS intervention: PTSD: n=5; anxiety: n=2; aggression: n=3). Beside an overall significant reduction in symptom levels over time (main effect of *Time*: *p*'s < .001, η^2_G's > .008), the active tDCS vs. sham groups did not significantly differ in symptom levels reductions, except for a slightly stronger reduction in PCL-5 scores in the active tDCS vs. sham group due to higher baseline PTSD symptoms levels in the active tDCS group (see **Table 2** and **Figure 2**). When the 3-months and 1-year follow-ups were taken into account, these results did not substantively change, see **Table 2**. PANAS Positive Affect and STAXI-2 Anger Expression and Control scales did not show significant effects of tDCS vs. sham (statistical results are reported in the Appendix).

EXPLORATORY ANALYSES ON THE RELATION BETWEEN INHIBITORY CONTROL AND SYMPTOM SEVERITY

At baseline, higher symptom severity on all scales significantly correlated with worse stop-signal task inhibitory control performance, see **Table 3**. Baseline no-go-accuracy significantly correlated with PCL-5 and BDI-II scores. No other baseline inhibitory control measure correlated significantly with symptom levels.

The overall improvement in SSRT or the achieved level of SSRT on session 5 did not significantly predict symptom reductions (all p's > .28, full statistical outcomes are reported in the Appendix). These results suggest no link between short-term inhibitory control improvements and symptom relief.

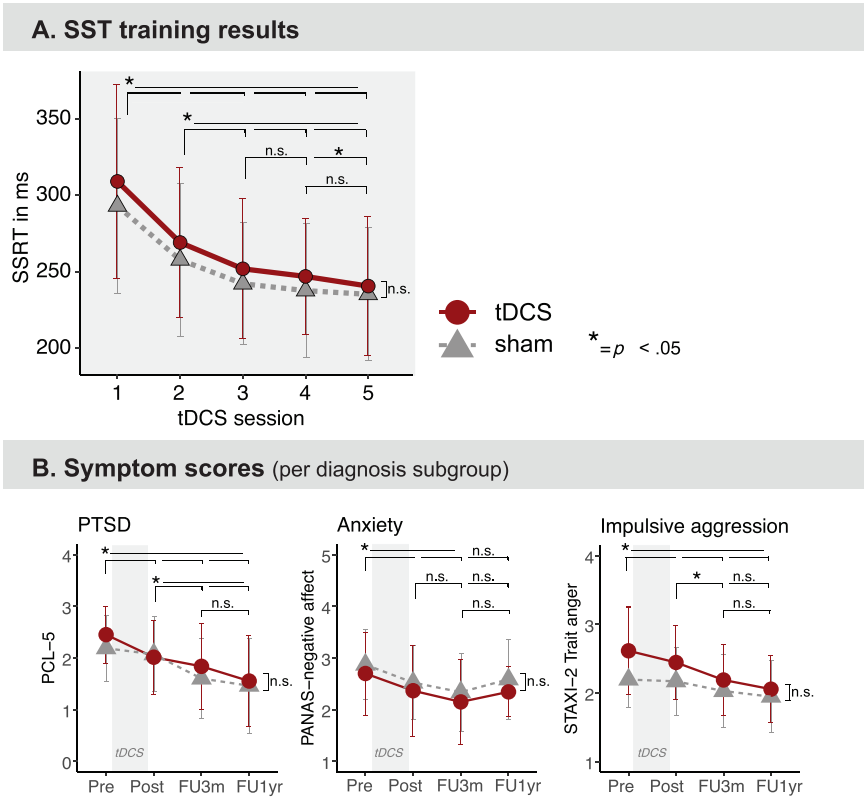

Figure 2. Mean SSRT **(A)** and mean item scores on symptom scales **(B)** ± SD per stimulation group. n.s. = non-significant. Please note that symptom scales were analyzed per subgroup of patients with the corresponding diagnosis, and that drop-out at follow-up reduced the sample sizes for FU-3m and FU-1yr assessments, see also **Table 2**. Exploratory analyses on the relation between inhibitory control and symptom severity

Table 3. Correlation matrix with baseline measures of symptom severity and inhibitory control.

	1	2	3	4	5	6	7
1. PCL-5							
2. PANAS Negative affect	.72**						
3. STAXI-2 Trait Anger	.31*	.33*					
4. BDI-II	.74**	.69**	.22*				
5. SSRT *(reversed)*	-.50**	-.33*	-.25*	-.36**			
6. Go/no-go: RT	-.04	.08	-.04	-.01	.04		
7. Go/no-go: no-go accuracy	-.27*	-.18	-.01	-.31*	.43**	.15	
8. IAT effect *(reversed)*	.15	.16	.01	.20	-.01	.16	.06

Higher symptom scores reflect higher symptom severity, lower (reversed) inhibitory control scores reflect worse inhibitory control performance. Note that the SSRT used for the baseline correlations was measured during the first tDCS session.
* $p < .05$, ** $p < .001$.

DISCUSSION

Inhibitory control is thought to play a role in symptoms of PTSD, anxiety and impulsive aggression. Here, the effects of a tDCS-combined inhibitory control training on pre-post measures of inhibitory control and symptoms were for the first time investigated in a preregistered RCT with a large clinical sample of military patients with these stress-related disorders. Contrary to previous findings[18], we failed to find an effect of anodal tDCS over the right IFG vs. sham on performance during the stop-signal task inhibitory control training. No support was found either for tDCS effects on post-intervention non-trained inhibitory control nor on symptom levels of PTSD, anxiety or impulsive aggression. Hence, despite positive effects of tDCS on inhibitory control in healthy individuals[14] and on symptoms of PTSD and anxiety in patients[46–48], we found no evidence to support that right IFG tDCS combined with inhibitory control training with our experimental set-up can effectively improve inhibitory control or stress-related symptoms in these patients. These results raise questions on why the tDCS effects on inhibitory control did not replicate in our clinical sample, and, subsequently, what may be more effective ways to modulate clinically relevant cognitive processes and stress-related symptoms with noninvasive brain stimulation.

EFFECTS OF TDCS-COMBINED TRAINING ON INHIBITORY CONTROL

A substantial body of single-session tDCS research[14,15] and a multiple-session tDCS-training intervention study[18] in healthy participants showed successful improvements in inhibitory control performance with tDCS settings not so different from ours (current intensity: 1-1.5 mA; anode over the right IFG; cathode on left orbital area or left cheek; duration: 10-30 min.). Compared to the study of Ditye and coworkers[18], we extended the training and stimulation duration per session. Yet, the effects of tDCS were not replicated. Perhaps by using a current density on the low end (0.036 mA/cm^2) of the range used for successful tDCS-enhanced stop-signal task performance in other studies (0.028 – 0.125 mA/cm^2)[14], the induced electrical field was too weak to modulate right IFG activity to an extent that would produce measurable behavioral changes (see e.g.[49]). On the other hand, higher current densities do not necessarily follow a linear increase of tDCS effectivity[12].

Secondly, although we used a montage as applied by other studies stimulating the IFG, there is uncertainty about the anode placement relative to the IFG. Simulations of the electrical field on one example brain showed a peak intensity located slightly above the IFG (see in the appendix: **Figure S.1.**). Although inconclusive, the target region may have received suboptimal stimulation. To more effectively target inhibitory control, the anode could be placed somewhat lower to better focus the electrical field on the right IFG, e.g., on 10/20 EEG positions F8 or F10[15,50], or higher, e.g., on position F4 to focus the field on the DLPFC[51,52]. However, tDCS with the anode placed on the F8-Cz Fz-T4 crossing, as in our study, has also shown successful response inhibition enhancement[14,15]. Technical tDCS parameter settings therefore do not seem to fully explain our null results.

Alternatively, we possibly over-trained a relatively simple inhibitory control task. As the primary physiological effects of tDCS act upon ongoing neuronal and synaptic activity[53–55], tDCS appears suitable to enhance processes that depend on synaptic plasticity, like learning and memory processes. Correspondingly, in Ditye's study[18], tDCS seemed to act as a necessary condition for an inhibitory control learning effect to occur. However, our extended training sessions produced clear learning curves in both stimulation groups, and we found no support for baseline inhibitory control performance to predict tDCS effectivity. Together with indications that tDCS-enhancement can supersede after experience-dependent learning (see e.g.[56]), this suggests that tDCS might have had little opportunity to further enhance training processes in our study. Moreover, patients with stress-related disorders may specifically show impulsivity in the emotional domain[57], and tDCS effects on cognitive and emotional outcomes seem to depend on active emotion regulation, cognitive effort and neural activity in the targeted area[13,58,59]. Our response inhibition training may have failed to adequately incorporate these factors due to its non-emotional nature and low cognitive load. Also non-trained inhibitory control tasks (go/no-go task and IAT) showed no evidence for tDCS effects, in line with expectations that effects do not transfer in the absence of tDCS effects on trained tasks[19]. Altogether, conditions for tDCS efficacy in these patients may crucially include emotionally challenging tasks during stimulation.

EFFECTS OF TDCS-COMBINED TRAINING ON SYMPTOMS

In light of the null-effects on inhibitory control, the tDCS intervention would not affect symptom levels of PTSD, anxiety and aggression via such mediating cognitive processes. On the other hand, tDCS effects on symptoms without concurrent cognitive improvement have previously been shown in depression[60] and PTSD patients[47], suggesting that prefrontal tDCS may also affect symptoms via other mechanisms. However, on stress-related as well as mood symptoms and general mental wellbeing, no evidence for tDCS effects was found. Possibly, such non-specific tDCS effects require more sessions and a shorter between-session-interval (max. 1 day)[61]. Patients in both stimulation groups did show significant symptom reduction over the course of the intervention, presumably as a result primarily of ongoing therapeutic processes of regular treatment.

FUTURE DIRECTIONS

To find more effective ways to target stress-related symptoms with tDCS, the next steps should be to identify what are the relevant brain processes that facilitate recovery, and to determine under what conditions tDCS effectively modulates those brain processes. Brain state may constitute one of the most important but also unresolved factors of influence on tDCS effectivity. Whereas we intended to attune brain states during the intervention across participants by applying a concurrent cognitive task, the combination with neuroimaging methods can help to better study brain state in parallel to the neural, behavioral and clinical effects of tDCS (see e.g.[59]). Regarding inhibitory control as a cognitive target, exploratory analyses confirmed the association with stress-related symptoms, but not with symptom relief. An alternative target may be tDCS over the DLPFC[62] to modulate working memory deficits

in stress-related disorders (see e.g.[63]) which can contribute to symptom relief[64]. Successful attempts to enhance effects of cognitive behavioral or exposure psychotherapy with prefrontal stimulation[48,59,65] also suggest that tDCS interventions might be further developed in existing clinical applications. More placebo-controlled clinical trials are encouraged to examine whether this is a viable option.

LIMITATIONS

Limitations in our study may restrict the generalization of our results. First, pre- and post-intervention measures were assessed online. As a trade-off for a lower travel burden for patients[66], this could have reduced the measurement sensitivity to detect (possibly weak) tDCS effects. On the other hand, cognitive assessment through online experiments appears reliable[67]. Also, we carried out this study in an (ex-)military, predominantly male sample. Excluding data from female participants did not essentially change the results, and our sample represented a broad and heterogeneous group, but military personnel in general may represent a relatively homogenous population due to rigid selection and training procedures. Our outcomes may therefore not directly translate to other populations.

CONCLUSION

The current RCT in military patients with stress-related symptoms provides no evidence for short-term or long-term benefits of 5 sessions of 20-minute tDCS targeting the right IFG at an intensity of 1.25 mA combined with response inhibition training, on inhibitory control or PTSD, anxiety and impulsive aggression symptoms. For these patients, tDCS may be more effective in higher doses (e.g., higher current density, more sessions) or when combined with emotionally challenging tasks or psychotherapy. Gaining insight in determinants of tDCS efficacy and convenient brain targets for neuromodulation in stress-related disorders will allow the tailoring of future tDCS interventions.

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Conflicts of Interest: None.

Appendix: Additional details on (analysis) methods and outcomes.

Data availability statement: The data that support the findings of this study are available from the corresponding author, FS, upon reasonable request.

REFERENCES

1. Straud CL, Siev J, Messer S, Zalta AK. Examining military population and trauma type as moderators of treatment outcome for first-line psychotherapies for PTSD: A meta-analysis. *Journal of Anxiety Disorders*. 2019;67:102133. doi:10.1016/j.janxdis.2019.102133

2. Spinhoven P, Batelaan N, Rhebergen D, van Balkom A, Schoevers R, Penninx BW. Prediction of 6-yr symptom course trajectories of anxiety disorders by diagnostic, clinical and psychological variables. *Journal of Anxiety Disorders*. 2016;44:92-101. doi:10.1016/j.janxdis.2016.10.011

3. Hayes JP, Hayes SM, Mikedis AM. Quantitative meta-analysis of neural activity in posttraumatic stress disorder. *Biology of Mood & Anxiety Disorders*. 2012;2(1):9. doi:10.1186/2045-5380-2-9

4. Davidson RJ, Putnam KM, Larson CL. Dysfunction in the neural circuitry of emotion regulation--a possible prelude to violence. *Science (New York, NY)*. 2000;289(2000):591-594. doi:10.1126/science.289.5479.591

5. Craske MG, Stein MB, Eley TC, et al. Anxiety disorders. *Nature Reviews Disease Primers*. 2017;3(1):17024. doi:10.1038/nrdp.2017.24

6. Etkin A, Gyurak A, O'Hara R. A neurobiological approach to the cognitive deficits of psychiatric disorders. *Dialogues in clinical neuroscience*. 2013;15(4):419-429.

7. DeGutis J, Esterman M, McCulloch B, Rosenblatt A, Milberg W, McGlinchey R. Posttraumatic Psychological Symptoms are Associated with Reduced Inhibitory Control, not General Executive Dysfunction. *Journal of the International Neuropsychological Society*. 2015;21(05):342-352. doi:10.1017/S1355617715000235

8. Aron AR, Robbins TW, Poldrack RA. Inhibition and the right inferior frontal cortex: One decade on. *Trends in Cognitive Sciences*. 2014;18(4):177-185. doi:10.1016/j.tics.2013.12.003

9. Aupperle RL, Melrose AJ, Stein MB, Paulus MP. Executive function and PTSD: Disengaging from trauma. *Neuropharmacology*. 2012;62(2):686-694. doi:10.1016/j.neuropharm.2011.02.008

10. van Rooij SJH, Jovanovic T. Impaired inhibition as an intermediate phenotype for PTSD risk and treatment response. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2019;89:435-445. doi:10.1016/j.pnpbp.2018.10.014

11. Marwood L, Wise T, Perkins AM, Cleare AJ. Meta-analyses of the neural mechanisms and predictors of response to psychotherapy in depression and anxiety. *Neuroscience & Biobehavioral Reviews*. 2018;95:61-72. doi:10.1016/j.neubiorev.2018.09.022

12. Yavari F, Jamil A, Mosayebi Samani M, Vidor LP, Nitsche MA. Basic and functional effects of transcranial Electrical Stimulation (tES)—An introduction. *Neuroscience & Biobehavioral Reviews*. 2018;85:81-92. doi:10.1016/j.neubiorev.2017.06.015

13. Smits FM, Schutter DJLG, van Honk J, Geuze E. Does non-invasive brain stimulation modulate emotional stress reactivity? *Social Cognitive and Affective Neuroscience*. 2020;15(1):23-51. doi:10.1093/scan/nsaa011

14. Mayer JT, Chopard G, Nicolier M, et al. Can transcranial direct current stimulation (tDCS) improve impulsivity in healthy and psychiatric adult populations? A systematic review. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2020;98:109814. doi:10.1016/j.pnpbp.2019.109814

15. Schroeder PA, Schwippel T, Wolz I, Svaldi J. Meta-analysis of the effects of transcranial direct current stimulation on inhibitory control. *Brain Stimulation*. Published online 2020. doi:10.1016/j.brs.2020.05.006

16. Zandbelt BB, Bloemendaal M, Hoogendam JM, Kahn RS, Vink M. Transcranial magnetic stimulation and functional MRI reveal cortical and subcortical interactions during stop-signal response inhibition. *Journal of Cognitive Neuroscience*. Published online 2013. doi:10.1162/jocn_a_00309

17. Alegria AA, Wulff M, Brinson H, et al. Real-time fMRI neurofeedback in adolescents with attention deficit hyperactivity disorder. *Human Brain Mapping*. Published online 2017. doi:10.1002/hbm.23584

18. Ditye T, Jacobson L, Walsh V, Lavidor M. Modulating behavioral inhibition by tDCS combined with cognitive training. *Experimental Brain Research*. 2012;219(3):363-368. doi:10.1007/s00221-012-3098-4

19. Berryhill ME, Martin D. Cognitive Effects of Transcranial Direct Current Stimulation in Healthy and Clinical Populations: An Overview. *Journal of ECT*. 2018;34(3):e25-e35. doi:10.1097/YCT.0000000000000534

20. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods*. 2007;39(2):175-191. doi:10.3758/BF03193146

21. First MB, Spitzer RL, Gibbon M, Williams JBW. Structured clinical interview for DSM-IV-TR axis I disorders, research version, patient edition. (SCID-I/P). In: *Biometrics Research*. New York State Psychiatric Institute; 2002.

22. Coccaro EF. Intermittent Explosive Disorder as a Disorder of Impulsive Aggression for DSM-5. *American Journal of Psychiatry*. 2012;169(6):577-588. doi:10.1176/appi.ajp.2012.11081259

23. Sheehan D V., Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. In: *Journal of Clinical Psychiatry*. Vol 59. ; 1998:22-33. doi:10.1016/S0924-9338(99)80239-9

24. Ambrus GG, Al-Moyed H, Chaieb L, Sarp L, Antal A, Paulus W. The fade-in – Short stimulation – Fade out approach to sham tDCS – Reliable at 1 mA for naïve and experienced subjects, but not investigators. *Brain Stimulation*. 2012;5(4):499-504. doi:10.1016/j.brs.2011.12.001

25. Marteau TM, Bekker H. The development of a 6-item short-form of the state scale of the Spielberger State Trait Anxiety Inventory (STAI). *British Journal of Clinical Psychology*. 1992;31:301-306.

26. Brunoni AR, Amadera J, Berbel B, Volz MS, Rizzerio BG, Fregni F. A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. *The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum (CINP)*. 2011;14(8):1133-1145. doi:10.1017/S1461145710001690

27. Logan GD, Cowan WB, Davis KA. On the ability to inhibit simple and choice reaction time responses: A model and a method. *Journal of Experimental Psychology: Human Perception and Performance*. 1984;10(2):276-291. doi:10.1037/0096-1523.10.2.276

28. Thoma P, Soria Bauser D, Suchan B. BESST (Bochum Emotional Stimulus Set)—A pilot validation study of a stimulus set containing emotional bodies and faces from frontal and averted views. *Psychiatry Research*. 2013;209(1):98-109. doi:10.1016/j.psychres.2012.11.012

29. Gladwin TE, Möbius M, Vink M. Threat-induced impulsivity in Go/Nogo tasks: Relationships to task-relevance of emotional stimuli and virtual proximity. *Consciousness and Cognition*. 2019;74:102795. doi:10.1016/j.concog.2019.102795

30. Greenwald AG, McGhee DE, Schwartz JLK. Measuring individual differences in implicit cognition: The implicit association test. *Journal of Personality and Social Psychology*. 1998;74(6):1464-1480. doi:10.1037/0022-3514.74.6.1464

31. Conrey FR, Sherman JW, Gawronski B, Hugenberg K, Groom CJ. Separating multiple processes in implicit social cognition: the quad model of implicit task performance. *Journal of personality and social psychology*. 2005;89(4):469-487. doi:10.1037/0022-3514.89.4.469

32. Singmann H, Kellen D. MPTinR: Analysis of multinomial processing tree models in R. *Behavior Research Methods*. 2013;45(2):560-575. doi:10.3758/s13428-012-0259-0

33. Weathers FW, Litz BT, Keane TM, Palmieri PA, Marx BP, Schnurr PP. The PTSD Checklist for DSM-5 (PCL-5). doi:10.1037/t02622-000

34. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. *J Pers Soc Psychol*. 1988;54(6):1063-1070. doi:10.1037/0022-3514.54.6.1063

35. Spielberger CD. *State-Trait Anger Expression Inventory-2: STAXI-2 Professional Manual*. FL: Psychological Assessment Resources.; 1999.

36. Beck, A. T., Steer, R. A., & Brown GK. *Beck Depression Inventory Manual (2nd Ed.).*; 1996.

37. Lambert MJ, Finch AE, Maruish ME. The Outcome Questionnaire. The use of psychological testing for treatment planning and outcomes assessment (2nd ed.). In: US: Lawrence Erlbaum Associates Publishers; 1999:831-869.

38. Bernstein DP, Stein JA, Newcomb MD, et al. Development and validation of a brief screening version of the Childhood Trauma Questionnaire. *Child Abuse & Neglect*. 2003;27(2):169-190. doi:10.1016/S0145-2134(02)00541-0

39. Patton JH, Stanford MS, Barratt ES. Factor structure of the Barratt impulsiveness scale. *Journal of clinical psychology*. 1995;51(6):768-774. doi:10.1002/1097-4679(199511)51:6<768

40. R Foundation for Statistical Computing. R: A language and environment for statistical computing. *R: A Language and Environment for Statistical Computing 331*. Published online 2016.

41. Kassambara A. rstatix: Pipe-Friendly Framework for Basic Statistical Tests. R package version 0.6.0.

42. Jaeger TF. Categorical data analysis: Away from ANOVAs (transformation or not) and towards logit mixed models. *Journal of Memory and Language*. 2008;59(4):434-446. doi:10.1016/j.jml.2007.11.007

43. Bates D, Mächler M, Bolker B, Walker S. Fitting Linear Mixed-Effects Models Using lme4. *Journal of Statistical Software*. 2015;67(1). doi:10.18637/jss.v067.i01

44. Dedoncker J, Brunoni AR, Baeken C, Vanderhasselt MA. A Systematic Review and Meta-Analysis of the Effects of Transcranial Direct Current Stimulation (tDCS) Over the Dorsolateral Prefrontal Cortex in Healthy and Neuropsychiatric Samples: Influence of Stimulation Parameters. *Brain Stimulation*. 2016;9(4):501-517. doi:10.1016/j.brs.2016.04.006

45. Jakobsen JC, Gluud C, Wetterslev J, Winkel P. When and how should multiple imputation be used for handling missing data in randomised clinical trials – a practical guide with flowcharts. *BMC Medical Research Methodology*. 2017;17(1):162. doi:10.1186/s12874-017-0442-1

46. Vicario CM, Salehinejad MA, Felmingham K, Martino G, Nitsche MA. A systematic review on the therapeutic effectiveness of non-invasive brain stimulation for the treatment of anxiety disorders. *Neuroscience and Biobehavioral Reviews*. 2019;96(August 2018):219-231. doi:10.1016/j.neubiorev.2018.12.012

47. Ahmadizadeh MJ, Rezaei M, Fitzgerald PB. Transcranial direct current stimulation (tDCS) for post-traumatic stress disorder (PTSD): A randomized, double-blinded, controlled trial. *Brain Research Bulletin*. 2019;153(September):273-278. doi:10.1016/j.brainresbull.2019.09.011

48. van 't Wout-Frank M, Shea MT, Larson VC, Greenberg BD, Philip NS. Combined transcranial direct current stimulation with virtual reality exposure for posttraumatic stress disorder: Feasibility and pilot results. *Brain Stimulation*. 2019;12(1):41-43. doi:10.1016/j.brs.2018.09.011

49. Li LM, Violante IR, Leech R, et al. Brain state and polarity dependent modulation of brain networks by transcranial direct current stimulation. *Human Brain Mapping*. 2019;40(3):904-915. doi:10.1002/hbm.24420

50. Coffman BA, Trumbo MC, Flores RA, et al. Impact of tDCS on performance and learning of target detection: Interaction with stimulus characteristics and experimental design. *Neuropsychologia*. Published online 2012. doi:10.1016/j.neuropsychologia.2012.03.012

51. Salehinejad MA, Wischnewski M, Nejati V, Vicario CM, Nitsche MA. Transcranial direct current stimulation in attention-deficit hyperactivity disorder: A meta-analysis of neuropsychological deficits. *PLoS ONE*. Published online 2019. doi:10.1371/journal.pone.0215095

52. Dousset C, Ingels A, Schröder E, et al. Transcranial Direct Current Stimulation Combined With Cognitive Training Induces Response Inhibition Facilitation Through Distinct Neural Responses According to the Stimulation Site: A Follow-up Event-Related Potentials Study. *Clinical EEG and Neuroscience*. Published online 2020. doi:10.1177/1550059420958967

53. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *The Journal of Physiology*. 2000;527(3):633-639. doi:10.1111/j.1469-7793.2000.t01-1-00633.x

54. Kronberg G, Bridi M, Abel T, Bikson M, Parra LC. Direct Current Stimulation Modulates LTP and LTD: Activity Dependence and Dendritic Effects. *Brain Stimulation*. 2017;10(1):51-58. doi:10.1016/j.brs.2016.10.001

55. Liebetanz D. Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability. *Brain*. 2002;125(10):2238-2247. doi:10.1093/brain/awf238

56. Fehring DJ, Illipparampil R, Acevedo N, Jaberzadeh S, Fitzgerald PB, Mansouri FA. Interaction of task-related learning and transcranial direct current stimulation of the prefrontal cortex in modulating executive functions. *Neuropsychologia*. 2019;131(April):148-159. doi:10.1016/j.neuropsychologia.2019.05.011

57. Johnson SL, Carver CS, Joormann J. Impulsive responses to emotion as a transdiagnostic vulnerability to internalizing and externalizing symptoms. *Journal of Affective Disorders*. 2013;150(3):872-878. doi:10.1016/j.jad.2013.05.004

58. Gill J, Shah-basak PP, Hamilton R. It's the Thought That Counts: Examining the Task-dependent Effects of Transcranial Direct Current Stimulation on Executive Function. *Brain Stimulation*. 2015;8:253-259. doi:10.1016/j.brs.2014.10.018

59. Nord CL, Halahakoon DC, Limbachya T, et al. Neural predictors of treatment response to brain stimulation and psychological therapy in depression: a double-blind randomized controlled trial. *Neuropsychopharmacology*. 2019;44(9):1613-1622. doi:10.1038/s41386-019-0401-0

60. Martin DM, Teng JZ, Lo TY, et al. Clinical pilot study of transcranial direct current stimulation combined with Cognitive Emotional Training for medication resistant depression. *Journal of Affective Disorders*. 2018;232:89-95. doi:10.1016/j.jad.2018.02.021

61. Alonzo A, Brassil J, Taylor JL, Martin D, Loo CK. Daily transcranial direct current stimulation (tDCS) leads to greater increases in cortical excitability than second daily transcranial direct current stimulation. *Brain Stimulation*. 2012;5(3):208-213. doi:10.1016/j.brs.2011.04.006

62. Brunoni AR, Vanderhasselt MA. Working memory improvement with non-invasive brain stimulation of the dorsolateral prefrontal cortex: A systematic review and meta-analysis. *Brain and Cognition*. 2014;86:1-9. doi:10.1016/j.bandc.2014.01.008

63. Scott JC, Matt GE, Wrocklage KM, et al. Quantitative meta-analysis of neurocognitive functioning in posttraumatic stress disorder. *Psychological Bulletin*. 2015;141(1):105-140. doi:10.1037/a0038039

64. Schweizer S, Samimi Z, Hasani J, Moradi A, Mirdoraghi F, Khaleghi M. Improving cognitive control in adolescents with post-traumatic stress disorder (PTSD). *Behaviour Research and Therapy*. 2017;93:88-94. doi:10.1016/j.brat.2017.03.017

65. Herrmann MJ, Katzorke A, Busch Y, et al. Medial prefrontal cortex stimulation accelerates therapy response of exposure therapy in acrophobia. *Brain Stimulation*. 2017;10(2):291-297. doi:10.1016/j.brs.2016.11.007

66. Smits FM, de Kort GJ, Geuze E. Acceptability of tDCS in treating stress-related mental health disorders: a mixed methods study among military patients and caregivers. *BMC Psychiatry*. 2021;21(1):1-12. doi:10.1186/s12888-021-03086-5

67. Gladwin TE, Vink M. Spatial anticipatory attentional bias for threat: Reliable individual differences with RT-based online measurement. *Consciousness and Cognition*. 2020;81:102930. doi:10.1016/j.concog.2020.102930

68. Thielscher A, Antunes A, Saturnino GB. Field modeling for transcranial magnetic stimulation: A useful tool to understand the physiological effects of TMS? In: *Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBS*. ; 2015. doi:10.1109/EMBC.2015.7318340

69. Greenwald AG, Rudman LA, Nosek BA, Banaji MR, Farnham SD, Mellott DS. A unified theory of implicit attitudes, stereotypes, self-esteem, and self-concept. *Psychological Review*. Published online 2002. doi:10.1037/0033-295X.109.1.3

70. Cisler JM, Koster EHW. Mechanisms of attentional biases towards threat in anxiety disorders: An integrative review. *Clinical Psychology Review*. Published online 2010. doi:10.1016/j.cpr.2009.11.003

71. McNally RJ. Attentional bias for threat: Crisis or opportunity? *Clinical Psychology Review*. Published online 2019. doi:10.1016/j.cpr.2018.05.005

72. Thoma P, Soria Bauser D, Suchan B. BESST (Bochum Emotional Stimulus Set)—A pilot validation study of a stimulus set containing emotional bodies and faces from frontal and averted views. Psychiatry Research. 2013;209(1):98-109. doi:10.1016/j.psychres.2012.11.012

APPENDIX

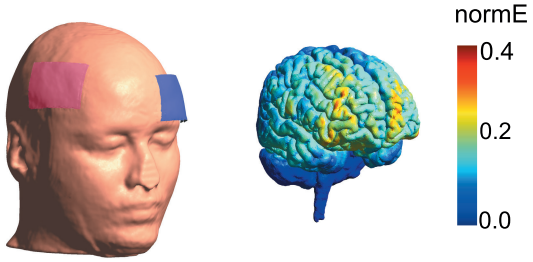


Figure S.1. A simulated induced electrical field image with the applied tDCS montage, created with SimNIBS 2.1[1].

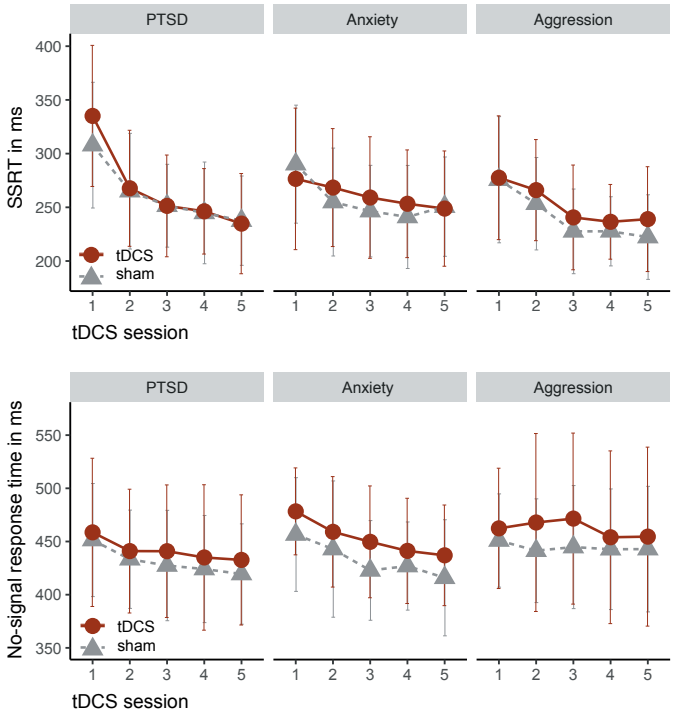


Figure S.2. Mean SSRT (above) and no-signal RT (below) ± SD per *Stimulation group* for each diagnosis subgroup. No-signal RT analysis results: When *Diagnosis* was entered into the model, the main and interaction effects of *Stimulation group* did not significantly change (p's > .180, η^2_G's < .018). In line with the SSRT outcomes, a significant *Time* × *Diagnosis* interaction appeared (p = .033, η^2_G = .007). In separate analyses of each diagnosis subgroup, PTSD and anxiety patients showed a significant main effect of *Time* (p's < .001, η^2_G's > .030), corresponding to decreasing RTs over sessions. No *Time* effect was observed in the impulsive aggression subgroup (p = .429, η^2_G = .004).

INFLUENCE OF BASELINE INHIBITORY CONTROL ON TDCS EFFECTS IN SST TRAINING

The SSRT change score (ΔSSRT = SSRT at session 5 – SSRT at session 1) was regressed on *pre-assessment Go/no-go scores* (RT and accuracy, separately) together with the predictor *Stimulation group,* and their interaction. The results are presented in **Table S.1.** *Go-RT* and *No-go accuracy* did not interact significantly with *Stimulation group* in predicting SSRT change, suggesting that baseline go/no-go performance did not influence tDCS effects on SSRT enhancement. No-go accuracy did have a main effect on SSRT change. Correlation analysis showed that lower no-go accuracy at baseline was associated with stronger SSRT improvements during training (r = .24, p = .036), implying that worse inhibitory control performance at baseline may leave more room for performance improvement during inhibitory control training.

Table S.1. Regression outcomes of models testing the predictive value of baseline go/no-go performance.

Predictor	*F* (df)	*p*-value
***Formula**: ΔSSRT ~ Stimulation group + Go-RT at pre-assessment*		
Stimulation group	0.25 (1)	.619
Go-RT	0.03 (1)	.854
Stimulation group × Go-RT	0.66 (1)	.418
***Formula**: ΔSSRT ~ Stimulation group + No-go accuracy at pre-assessment*		
Stimulation group	0.26 (1)	.610
No-go accuracy	4.69 (1)	.033
Stimulation group × No-go accuracy	0.01 (1)	.933

IAT – QUAD MODEL DETAILS AND OUTCOMES

The Quad model[2] includes the following components that drive response behavior in the IAT: association activation (AC: "the likelihood that automatic bias is activated by a stimulus"), discriminability (D: "the likelihood that a correct response can be determined"), overcoming bias (OB: "the likelihood that automatic bias is overcome"), and guessing (G: "the likelihood that, in the absence of other information, a guessing bias drives responses). The D and G parameters were defined for target words and attribute words separately (i.e., for target words: D_{target} and G_{target}, and for attribute words: $D_{attribute}$ and $G_{attribute}$). A single parameter was defined for AC and OB, as bidirectional associations were assumed[3]. The model was fitted on the number of correct and incorrect responses per trial category and task phase from all participants, separately for the pre- and post-assessment and for the active tDCS and sham groups.

To test group differences in the overcoming bias (OB) parameter at post-assessment, we tested the free model (for parameter estimations, see **Table S.2.**) against a model where OB was constrained to $OB_{tDCS} = OB_{sham}$ in a loglikelihood ratio test. The model fit improved very little (ΔAIC = -1.09), indicating that the OB parameter did not differ significantly between groups

post-intervention. To test changes in OB over time in both groups, we tested the free model against a model where OB was constrained to $OB_{Pre} = OB_{Post}$. This slightly reduced model fit in both stimulation groups as reflected by small increases in Akaike's Information Criterion (ΔAIC) (tDCS group: ΔAIC = +3.83, sham group: ΔAIC = +0.54), indicating that OB changed from pre-to-post intervention. OB decreased over time, representing reduced implicit inhibitory control, see **Table S.2.**

Table S.2. Quad model parameters for latent variables underlying IAT performance.

	tDCS				**Sham**			
	Pre-assessment		***Post-assessment***		***Pre-assessment***		***Post-assessment***	
Parameter	*Estimate*	*CI -95%*	*Estimate*	*CI -95%*	*Estimate*	*CI -95%*	*Estimate*	*CI -95%*
AC	.41	[.17, .64]	.11	[-.12, .33]	.14	[-.16, .45]	.13	[-.10, .37]
D_{target}	.94	[.92, .95]	.91	[.89, .93]	.95	[.94, .97]	.91	[.89, .93]
$D_{attribute}$	.96	[.95, .98]	.93	[.91, .94]	.95	[.93, .97]	.94	[.92, .96]
G_{target}	.52	[.42, .63]	.50	[.42, .57]	.54	[.42, .65]	.47	[.39, .55]
$G_{attribute}$	.61	[.47, .75]	.64	[.56, .73]	.44	[.32, .55]	.50	[.40, .61]
OB	1.00	[.96, 1.04]	.69	[-.17, 1.52]	.84	[.39, 1.28]	.58	[-.30, 1.45]

DOT-PROBE TASK

The dot-probe task measures attentional biases for threat. In this task, a pair of face cues (one angry face and one neutral face) were presented on a computer screen, divided over the upper and lower half of the screen. After a variable cue-stimulus interval (CSI; 200, 400, 600, 900 or 1200 ms), the face cues were replaced by a probe stimulus ('>>>' or '<<<') and a distractor stimulus ('\/\/' or '/\/\'). Participants were instructed to identify the direction of the probe stimulus (left or right) as fast as possible by pressing the correct button on the keyboard: 'F' or 'J'. The probe stimulus randomly appeared in the angry face cue location or in the neutral face cue location. An attentional bias toward the threat (here: angry face) location is induced by the fast attention capture of threat cues, especially at short CSIs[4]. A threat avoidance bias is also found in PTSD and anxiety patients, especially at longer CSIs. The attentional bias is computed as the RT difference between stimuli in the threat vs. neutral location (RT threat – RT neutral). The dot-probe task was only assessed post-intervention.

Results. Data were not available for 8 participants who did not complete the dot-probe task, leaving a sample of 88 for attention bias analysis (42 active tDCS, 46 sham). The attentional bias scores across CSI durations showed a very low split-half reliability of $r = -0.10$. This is not surprising in light of recent insights: dot-probe performance does often not reliably measure attentional bias[5], although this task has also shown reliable results (see e.g.[6]). Considering that the tDCS intervention could have modulated aspects of dot-probe task performance, we carried out the preregistered analysis in spite of the low reliability.

Overall, both active tDCS and sham groups showed very small attentional bias scores that did not significantly differ from zero (attentional bias score in ms – active tDCS: M = 5.3 ±27.7; sham: -1.4 ±25.1). Regardless of controlling for *Age* and *Medication use*, the attentional bias scores were not significantly influenced by *Stimulation group* or *CSI duration* (all *p*'s > .38), see **Table S.3.**

Table S.3. Attentional bias scores (mean ±standard deviation) and analysis results

	CSI	Attentional bias score	Effect	*p*	η^2_G
Active tDCS	200 ms	-5.4 ±81.5	*Stimulation group*	.629	.001
	400 ms	-17.1 ±68.4	*CSI*	.386	.011
	600 ms	17.2 ±87.6	*Stimulation group* × *CSI*	.756	.005
	900 ms	-1.5 ±70.2			
	1200 ms	-8.1 ±73.0			
Sham	200 ms	-0.3 ±84.8			
	400 ms	-10.4 ±70.4			
	600 ms	11.9 ±72.2			
	900 ms	1.7 ±80.1			
	1200 ms	1.7 ±73.1			

PANAS POSITIVE AFFECT AND STAXI-2 ANGER CONTROL SUBSCALES RESULTS

PANAS Positive Affect. There were no significant main effects of *Stimulation group* or *Time* (*p*'s > .19) on Positive Affect scores, and no significant *Stimulation group* × *Time* interaction effect ($p = .244$, $\eta^2_G = .006$).

STAXI-2 Anger Expression and Control. For the STAXI-2 Anger Expression scales, only the interaction *Time* × *Subscale* was significant ($p < .001$, $\eta^2_G = .019$). As expected, the Expression subscale scores decreased from pre- to post-assessment, indicating a reduction in anger expression (mean item scores – Anger Expression Out: M_{pre} ±SD = 2.5 ±0.5, M_{post} = 2.3 ±0.5; Anger Expression In: M_{pre} = 2.4 ±0.5, M_{post} = 2.4 ±0.5). Instead, the Control subscale scores increased, indicating more anger control (Anger Control Out: M_{pre} ±SD = 2.1 ±0.6, M_{post} = 2.3 ±0.5; Anger Control In: M_{pre} = 2.2 ±0.6, M_{post} = 2.5 ±0.5). Pairwise comparisons showed that the Express Anger Out subscale significantly decreased from pre- to post-assessment ($p = .018$), and from post-assessment to the 1-year follow-up ($p = .006$). The Express Anger In subscale did not significantly change between subsequent measurements (all *p*'s > .120). Scores on the Control Anger In and Control Anger Out subscales significantly increased from pre- to post-assessment (respectively: $p = .021$, $p = .043$), but showed no further change to the follow-ups at 3 months and 1 year (*p*'s > .100). The interaction effects of interest, *Stimulation group* × *Time* ($p = .533$) and *Stimulation group* × *Time* × *Subscale* ($p = .743$) were not significant.

EXPLORATORY ANALYSES – STATISTICAL OUTCOMES OF REGRESSION MODELS

Table S.4. Regression outcomes of models testing the predictive value of SSRT improvement.

Formula: Δsymptom score ~ Stimulation group + ΔSSRT

Predictor	*F* (df)	*p*-value
Outcome: Δsymptom score PCL-5		
Stimulation group	1.43 (1)	.235
ΔSSRT	**0.30 (1)**	**.583**
Outcome: Δsymptom score PANAS Negative Affect		
Stimulation group	0.01 (1)	.936
ΔSSRT	**0.05 (1)**	**.818**
Outcome: Δsymptom score STAXI-2 Trait Anger		
Stimulation group	2.48 (1)	.119
ΔSSRT	**1.18 (1)**	**.280**

Table S.5. Regression outcomes of models testing the predictive value of achieved SSRT level on session 5.

Formula: Post-assessment symptom score ~ Stimulation group + pre-assessment symptom score + SSRT on session 5

Predictor	*F* (df)	*p*-value
Outcome: Post-assessment symptom score PCL-5		
Pre-assessment symptom score PCL-5	225.10 (1)	<.001
Stimulation group	2.27 (1)	.135
SSRT on session 5	**0.00 (1)**	**.980**
Outcome: Post-assessment symptom score PANAS Negative Affect		
Pre-assessment symptom score PANAS Negative Affect	120.09 (1)	<.001
Stimulation group	0.34 (1)	.562
SSRT on session 5	**0.17 (1)**	**.680**
Outcome: Post-assessment symptom score STAXI-2 Trait Anger		
Pre-assessment symptom score STAXI-2 Trait Anger	175.02	<.001
Stimulation group	0.09 (1)	.761
SSRT on session 5	**0.510 (1)**	**.477**

REFERENCES

1. Thielscher A, Antunes A, Saturnino GB. Field modeling for transcranial magnetic stimulation: A useful tool to understand the physiological effects of TMS? In: 2015 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC). IEEE; 2015:222-225. doi:10.1109/EMBC.2015.7318340

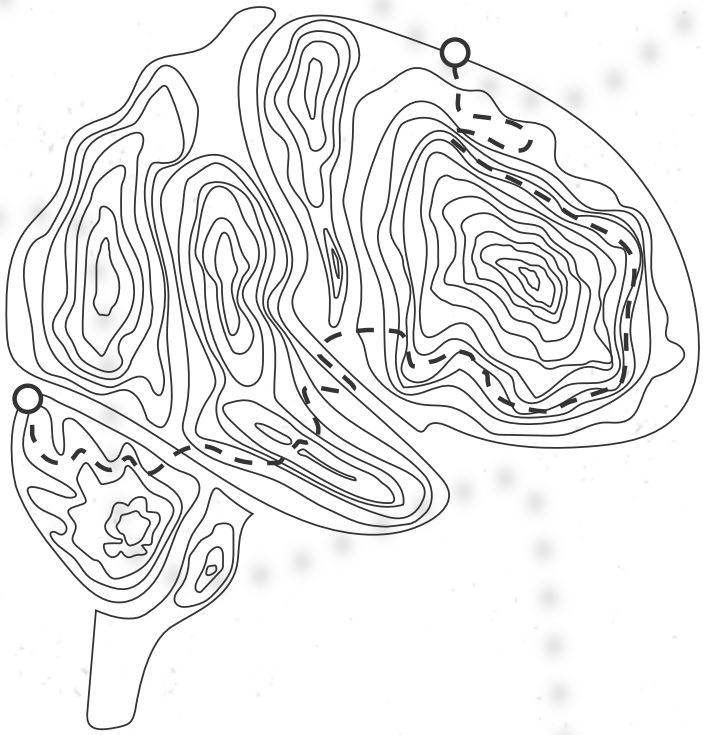
2. Conrey FR, Sherman JW, Gawronski B, Hugenberg K, Groom CJ. Separating multiple processes in implicit social cognition: the quad model of implicit task performance. *J Pers Soc Psychol.* 2005;89(4):469-487. doi:10.1037/0022-3514.89.4.469

3. Greenwald AG, Rudman LA, Nosek BA, Banaji MR, Farnham SD, Mellott DS. A unified theory of implicit attitudes, stereotypes, self-esteem, and self-concept. *Psychological Review*. Published online 2002. doi:10.1037/0033-295X.109.1.3

4. Cisler JM, Koster EHW. Mechanisms of attentional biases towards threat in anxiety disorders: An integrative review. *Clinical Psychology Review*. Published online 2010. doi:10.1016/j.cpr.2009.11.003

5. McNally RJ. Attentional bias for threat: Crisis or opportunity? *Clinical Psychology Review.* Published online 2019. doi:10.1016/j.cpr.2018.05.005

6. Gladwin TE, Vink M. Spatial anticipatory attentional bias for threat: Reliable individual differences with RT-based online measurement. *Consciousness and Cognition*. 2020;81:102930. doi:10.1016/j.concog.2020.102930



CHAPTER 4

Acceptability of tDCS in treating stress-related mental health disorders: A mixed methods study among military patients and caregivers

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ABSTRACT

Background: Noninvasive brain stimulation techniques like transcranial direct current stimulation (tDCS) offer potential new approaches to treat stress-related mental health disorders. While the acceptability of tDCS as a treatment tool plays a crucial role in its development and implementation, little is known about tDCS acceptability for users in mental healthcare, especially in the context of stress-related disorders.

Methods: Using a mixed-methods approach, we investigated tDCS acceptability among 102 active duty and post-active military patients with stress-related symptoms (posttraumatic stress disorder, anxiety and impulsive aggression) who participated in a 5-session tDCS intervention. Quantitative dropout and adverse effects data were collected for all patients involved in the sham-controlled tDCS intervention. We additionally explored perspectives on the acceptability of tDCS treatment via a theory-based semi-structured interview. A subgroup of patients as well as their caregivers were interviewed to include the views of both patients and mental healthcare professionals.

Results: Quantitative outcomes showed minimal tDCS-related adverse effects (mild itching or burning sensations on the scalp) and high tDCS treatment adherence (dropout rate: 4% for active tDCS, 0% for sham). The qualitative outcomes showed predominantly positive attitudes towards tDCS interventions for stress-related disorders, but only as complementary to psychotherapy. Remarkably, despite the perception that sufficient explanation was provided, patients and caregivers stressed that tDCS treatment comprehension was limited and should improve. Also, the travel associated with frequent on-site tDCS sessions may produce a significant barrier to care for patients with stress-related disorders and active-duty military personnel.

Conclusions: Acceptability numbers and perspectives from military patients and caregivers suggest that tDCS is an acceptable complementary tool in the treatment of stress-related disorders. Critically, however, if tDCS is to be used beyond scientific studies, adequately educating users on tDCS working mechanisms is vital to further improve its acceptability. Also, the perceived potential barrier to care due to frequent travel may favor home-based tDCS solutions.

BACKGROUND

More than one third of patients with stress-related mental health disorders like posttraumatic stress disorder (PTSD) and anxiety do not benefit from current evidence-based treatments[1,2], military patients in particular[3–5]. Noninvasive brain stimulation with transcranial magnetic (TMS) or direct current stimulation (tDCS) provides potential add-on treatments or may facilitate effects of pharmacological or psychological therapies[6]. Of these techniques, tDCS might be most suitable to apply in outpatient clinical and military contexts; it is a portable technique, has a better safety profile, and is easier in use[7]. Accordingly, interest for tDCS in the fields of PTSD and anxiety is growing (see e.g.[8,9]). However, while ongoing studies aim to quantify and optimize tDCS effectivity, the acceptability of tDCS has received remarkably little attention. Especially in the area of stress-related disorders, patients can be particularly skeptical towards alternative treatment approaches[10,11] and may show lower treatment adherence as a result[12]. Also the views of mental healthcare professionals on tDCS treatment play an important role in its overall acceptability[13]. Hence, it is necessary to understand the acceptability of tDCS as a treatment tool from the perspective of this particular patient population and their caregivers.

TDCS is commonly administered by applying a weak current (~ 1.0 - 2.5 mA) for 10-40 minutes between two electrodes placed over the scalp, leading to modulation of neural excitability and plasticity in the underlying cortex[14]. Psychiatric tDCS interventions are often aimed at improving disrupted neurobiological processes involved in (working) memory and emotion regulation[15,16] and usually comprise 5-30 tDCS sessions applied with an interval of one or several days[17].

Other psychiatric populations show relatively high acceptability for tDCS interventions; investigations among patients with depression, substance use disorders or schizophrenia show that tDCS associated adverse events commonly occur only in a minority of tDCS participants (0-40%) and are restricted to relatively mild sensations including itching, tingling or headache[18]. Dropout rates are low (6-12%[19,20]) – especially when compared to dropout rates for standard stress-related disorder treatments (e.g., exposure-based psychotherapy: 18-50%[21–24]). The main reasons for dropout are the adverse side effects and missing treatment sessions.

Beside such quantitative measures, a minor body of qualitative research into the acceptability of tDCS is available, conducted in the context of tDCS interventions for stroke rehabilitation and HIV-related depression[25–28]. Here, tDCS participants reported to be satisfied overall with undergoing a tDCS intervention. Yet, the patients also reported to feel some hesitancy towards future tDCS use because of the inflexible tDCS treatment schemes, and burning, itching or painful tDCS sensations (which in general bother patients more than healthy tDCS participants[29]). Importantly, these and other user experiences with novel treatment tools like tDCS can heavily impact its treatment success; the patients' perspectives on the intervention's

acceptability drive how much they will engage in and adhere to the intervention, and the caregivers' perspectives partly determine if and how the intervention will be delivered[13,30]. Early recognition of barriers associated with novel healthcare interventions such as tDCS therefore allows early optimization and cost-effective implementation of the intervention[31].

Because the acceptability of an intervention is formed through complex (social) interactions between patient, caregiver and technology, this concept is hard to study with quantitative research methods alone[32]. Instead, qualitative examination allows to comprehensively investigate views on the acceptability of a novel intervention. A validated theoretical ground for qualitative assessment of acceptability is offered by the Theoretical Framework of Acceptability (TFA) drafted by Sekhon and colleagues[33]. The TFA is based on extensive research among patients and caregivers[30]. Acceptability is described as: *"the acceptability of an intervention is determined by the appropriateness of addressing the clinical problem, by how well an intervention is suited to an individual lifestyle and how convenient the intervention is able to treat a medical problem"* (Sekhon et al. (2017)[34], page 6). **Figure 1** displays the seven key components that drive acceptability according to the TFA. Using the TFA in qualitative research can thus provide insights in the different aspects of acceptability and underlying reasons, and can be applied to assess the patient's and the caregiver's perspective in a similar way.

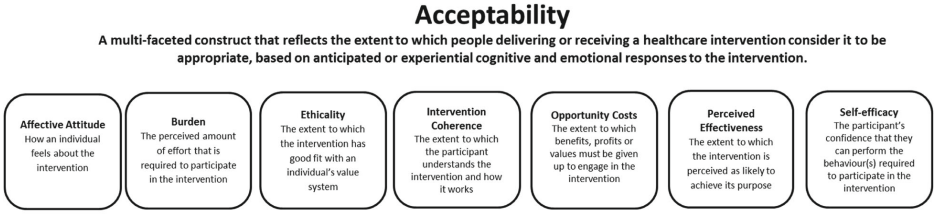

Figure 1. The Theoretical Framework of Acceptability (TFA)[30]. Reproduced under the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

Here, we studied the acceptability of tDCS for military patients who underwent a tDCS intervention during a period of regular treatment for stress-related disorders like PTSD, anxiety or impulsive aggression. To provide both comparative quantitative measures as well as comprehensive insights into the acceptability of tDCS as a treatment tool, we used a mixed methods approach that draws from the strengths of both quantitative and qualitative methods[35]; next to quantifying acceptability in terms of dropout rates and adverse events, we conducted an exploratory study using semi-structured interviews based on the key drivers of the TFA[33] in a subgroup of the participants. Unlike other tDCS acceptability studies, we also included caregivers in the qualitative study to simultaneously gain understanding of the health care professional's perspectives on tDCS as a treatment tool.

METHOD

PARTICIPANTS AND DATA ACQUISITION

This study was carried out in parallel to a randomized controlled trial (RCT) investigating the effects of prefrontal tDCS combined with cognitive training on PTSD, anxiety and impulsive aggression symptoms. RCT participants were military servicemen and veterans (22-60 years old) of the Dutch Ministry of Defence who received treatment for PTSD, an anxiety disorder or impulsive aggression. Patients with a predominant major depressive disorder diagnosis, a psychotic disorder diagnosis or a history of neurological complaints were excluded from participation. Patients participated in the tDCS intervention between May 2016 and October 2019. The study adhered to CONSORT guidelines where applicable. More details on the RCT protocol were pre-registered at the Netherlands Trial Register (ID: NL5709).

Interview respondents and setting

For the qualitative interview study, RCT participants with recent tDCS experience were recruited. Participants were interviewed in the months after they underwent the tDCS intervention (mean time between the tDCS intervention and the interview: 5 months and 4 weeks; range: 1-10 months). We only approached patients who received active tDCS (i.e., no participants from the sham (placebo) condition). Caregivers were recruited among psychologists and psychiatrists from the Dutch military mental healthcare organization who were informed about the tDCS intervention and had treated at least one patient who participated in the tDCS intervention. Interviews were carried out between April and August 2019 and took place at a time and place of the respondent's preference, usually at the respondent's home or workplace. Respondents were offered a 10-euro gift card for participation.

THE TDCS INTERVENTION

The tDCS intervention in the RCT comprised five tDCS sessions divided over two weeks, at the University Medical Center Utrecht, the Netherlands. Patients were allocated to the active tDCS or sham tDCS condition in a 1:1 ratio, based on a MATLAB-generated simple randomization sequence list with codes to activate the DC-stimulator for active or sham tDCS (blind to experimenters and patients). In each session, prefrontal tDCS was applied for 20 minutes (active) or 16 seconds (sham), at 1.25 mA, with two 5×7 cm electrodes (anode over the right inferior frontal gyrus (IFG), cathode over the left orbital area). During tDCS, patients performed a stop-signal task[36] on a computer for 30 minutes. Performing the stop-signal task served to activate the tDCS target region (right IFG) and train the cognitive function of inhibitory control. The aim of this tDCS-cognitive training combination was to reduce symptom levels by improving underlying deficits in (the neural network of) inhibitory control over exaggerated or inappropriate behavioral responses (see e.g.,[37,38]). Importantly, although the application of tDCS was always combined with stop-signal task training, the measures assessed in this study

focused on the experiences with tDCS. The total duration of each tDCS session was max. one hour. All patients received the tDCS intervention in parallel to regular treatment.

DATA COLLECTION

Quantitative data collection

For all patients participating in the RCT, we collected data from three quantitative acceptability indicators: dropout rates, adverse effects and changes in emotional state.

(i) Dropout rate (as an indicator of treatment adherence)

Dropout was defined as not completing the tDCS intervention after starting the first tDCS session.

(ii) Adverse effects of tDCS (as an indicator of treatment burden)

After each tDCS session, patients filled in the tDCS adverse effects questionnaire[18] on 4-point Likert scales to which extent they had experienced twelve possible tDCS side effects (from 1: "absent" to 4: "severe"), and to which extent they attributed each experienced side effect to tDCS (from 1: "not at all" to 4: "completely"). Also, perceived current strength and tDCS comfort were rated on a 10 cm VAS line with the anchors 0: "Very weak / uncomfortable" and 10: "Very strong / comfortable". Adverse events occurring outside the research visits were systematically evaluated at each session by asking a description of the adverse event, the adverse event duration, and its severity (1: "mild", 2: "moderate", 3: "severe" or 4: "life-threatening").

(iii) Changes in emotional state (as an indicator of treatment attitude)

Directly before and after each tDCS session, six emotional state items from the STAI-6 questionnaire[39] were rated by the patient from 1: "Not at all" to 4: "Very much".

Qualitative data

Qualitative data were gathered through semi-structured interviews based on the seven key drivers of the TFA[33]. Interviews were held until data saturation was reached. All interviews were recorded with an Olympus VN-8100PM recorder and transcribed verbatim. Written field-notes containing contextual information (e.g., events happening during the visit) served as additional data source. Interviews lasted on average 31 minutes.

We used the 'framework method'[40] to analyze the interview data. This systematic and flexible approach for analyzing qualitative data is an iterative process including the following steps: familiarizing with the data by carefully reading the transcripts, deductive coding of concepts in the transcripts according to pre-defined codes (here: based on the TFA key drivers), and

inductive coding of concepts in the transcripts by acknowledging emerging new concepts[41]. Two independent other researchers compared our drafted coding scheme to the transcripts. We adapted the coding scheme where needed. A final coding scheme or 'analytical framework'[40] was defined according to which all transcripts were coded (see Appendix). The coding process was carried out in the qualitative coding software NVivo. **Table 1** illustrates an example of the coding process.

Table 1. Example of the coding process.

Meaningful quote from interview transcript	Pre-defined code	Sub-code	Description
"… I'm not sure if this is going to help me deal with the problem." [P4]	Ethicality	Relationship between tDCS and symptoms	Comments on how the intervention method fits to the experienced symptoms.
"I'm not much of a talker, so this suits me." [P1]		Comparison with other therapies	Comments on how well the intervention fits, compared to other treatments.

RESULTS

QUANTITATIVE RESULTS

As depicted in **Figure 2**, of the 102 included patients in the tDCS intervention in the RCT, 2 patients in the active tDCS treatment condition dropped out (for reasons, see **Table 2**). None of the patients in the sham condition dropped out. Hence, treatment adherence was high in both groups.

TDCS side effects during the sessions were on average scored as "absent" or "mild". Of the side effects that were most frequently experienced, the effects that were most strongly attributed to tDCS were: burning, itching and tingling sensations on the scalp (mean attribution score = 3.1). Patients who received active tDCS (vs. sham tDCS) also reported these side effects more frequently (see **Table 2**) and scored them as slightly more severe (see **Figure 3**). Other frequently reported side effects like difficulty concentrating, head ache and sleepiness were also attributed to tDCS, but to a lesser extent (mean attribution score = 2.2) and with a similar incidence across active tDCS and sham groups. All adverse events happening outside of the tDCS sessions that were possibly related to the intervention and reported by more than one participant are listed in **Table 2**. Adverse events had on average a mild to moderate severity. Head ache after the session was the most prevalent adverse event in both the active tDCS and sham groups (mean incidence: 42%). Patients also experienced fatigue (more frequently in the active tDCS group) and an emotionally or physically "tense" feeling (more frequently in the sham group) after the session. Short periods of dizziness (max. 30 minutes after the session) were also reported by a minority of patients (9% of all patients, reported more frequently in the sham group). Together these numbers indicate a relatively low burden of adverse events in

the tDCS intervention. Compared to the placebo treatment (sham tDCS) the additional adverse events associated with the real treatment (active tDCS) were very limited.

The average changes in self-reported emotional state (STAI-6) during the tDCS sessions were negligible, see **Table 2**. This may indicate a neutral attitude of the patients toward the tDCS treatment; the tDCS sessions did not depress or elevate their mood.

The raw data underlying these numbers is provided online.

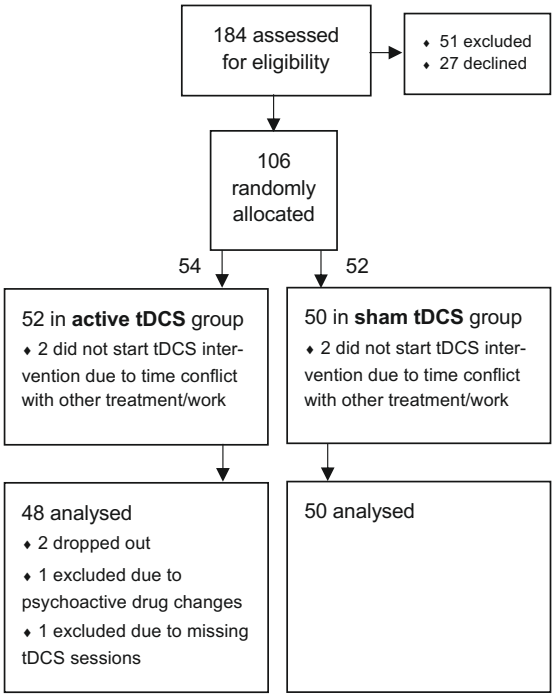

Figure 2. RCT study flow.

Table 2. Outcomes of the tDCS side effects questionnaire, STAI-6, adverse events and dropout: incidence rates and mean item scores.

Dropout rate

tDCS	**4% (n = 2)**	**Reasons:** • The first dropout patient got a mild panic attack before the first session, during the tDCS work-up procedure to familiarize participants with tDCS sensations. He preferred to quit the intervention afterwards. • The second dropout patient was admitted to an intensive in-house therapy after the second tDCS session, preventing him from finishing the remaining tDCS sessions of the intervention.
Sham	**0% (n = 0)**	

Side effects during tDCS sessions (self-report questionnaire)

		Acute change in mood	Burning	Difficulty concentrating	Dizziness	Headache	Itching	Nausea	Neck pain	Pain on the skull	Red skin after session	Sleepiness	Tingling
Incidence (severity score > 1)	*tDCS*	18%	46%	67%	16%	29%	55%	4%	19%	11%	3%	55%	54%
	Sham	16%	29%	69%	11%	27%	30%	4%	19%	9%	6%	44%	49%
Attribution to tDCS	*tDCS*	2,5	3,4	2,1	2,8	2,5	3,3	2,5	1,8	2,9	3,5	2,4	3,1
	Sham	2,2	3,0	1,8	2,8	2,1	2,9	3,4	1,5	2,7	3,2	1,9	3,1

Current strength and comfort during tDCS sessions (self-report questionnaire)

	Perceived current strength	SD	Comfort	SD
tDCS	**3,5**	2,5	**6,2**	2,2
Sham	**2,4**	2,2	**6,8**	2,2

Adverse events outside the research visits (researcher reports)

		Head ache	Nausea	Dizziness	Fatigue	Insomnia	Feeling tense	Depressed mood	Red/sensitive skin at electrode site
Incidence	*tDCS*	43%	4%	6%	28%	4%	11%	6%	8%
	Sham	41%	8%	12%	14%	8%	20%	6%	4%
Severity		1,5	1,6	1,5	1,9	1,7	1,8	1,8	1,2
Duration		<1 day	<1 day	<1 day	<1 day	2-3 days	<1 day	1-2 days	<1 day

Change in emotional state from pre- to post-session (STAI-6)

	Calm	SD	Tense	SD	Upset	SD	Relaxed	SD	Content	SD	Worried	SD
tDCS	**-0,1**	0,4	**0**	0,4	**0**	0,2	**0**	0,4	**-0,1**	0,3	**-0,1**	0,2
Sham	**-0,1**	0,3	**+0,1**	0,3	**+0,1**	0,2	**-0,1**	0,3	**0**	0,3	**-0,1**	0,2

SD = standard deviation.

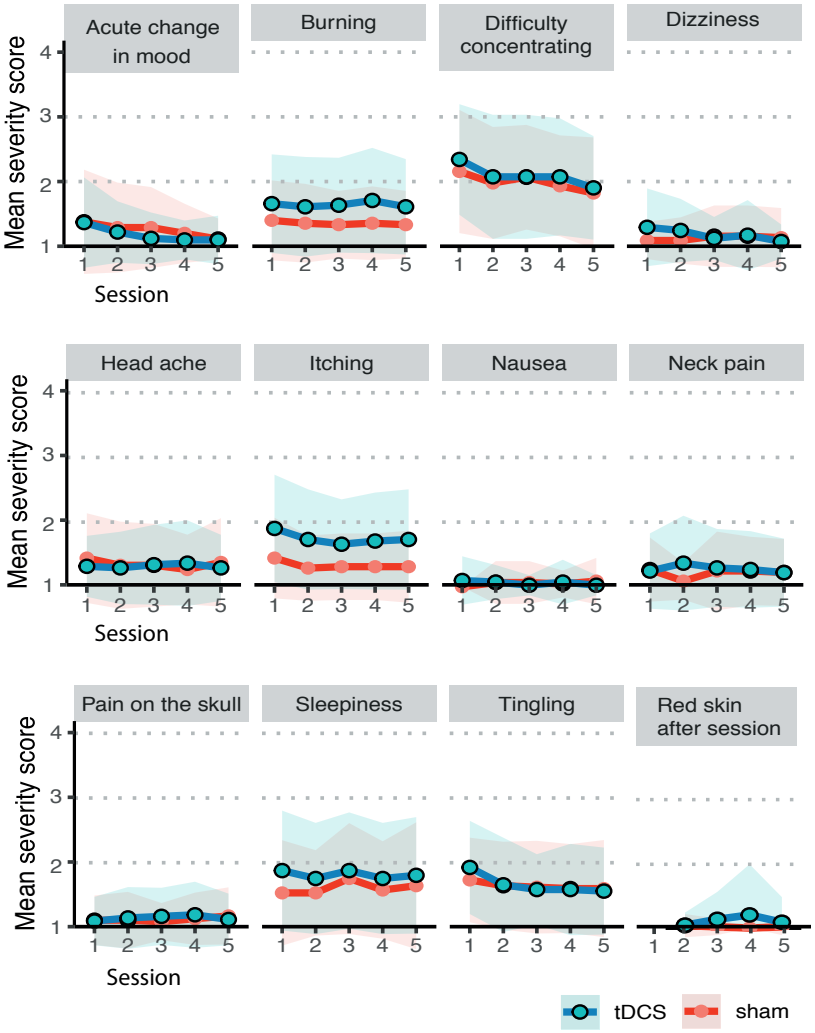

Figure 3. Mean item severity scores on the tDCS adverse side effects questionnaire (ribbon: ± standard deviation).

INTERVIEW RESPONDENTS

After interviewing 7 patients (3 post-active veterans, 4 active-duty military personnel, age: 26-58 years) and 5 caregivers (age: 27-57 years) data collection was discontinued; the last interviews yielded no new themes among patients or caregivers. For an overview of respondent characteristics, see **Table 3**.

Table 3. Demographic and clinical respondent characteristics

PATIENTS				CAREGIVERS		
Respondent number	**Sex**	**Diagnosis**	**Current treatment**	**Respondent number**	**Sex**	**Profession**
P1	male	PTSD	Pharmacological treatment	**CG1**	female	Psychologist
P2	male	Aggression regulation problems	Pharmacological treatment, CBT	**CG2**	male	Psychologist
P3	male	Anxiety	CBT	**CG3**	female	Psychologist
P4	male	Anxiety, Depression	CBT	**CG4**	male	Psychologist
P5	male	Anxiety, PTSD, Depression	Pharmacological treatment, CBT	**CG5**	male	Psychiatrist
P6	male	PTSD, Aggression regulation problems	EMDR			
P7	male	Aggression regulation problems	CBT			

CBT = cognitive behavioral therapy; EMDR = eye-movement desensitization and re-processing therapy.

INTERVIEW RESULTS

The interview results are presented below per key driver of the TFA.

i) **Affective Attitude**

Most patients and caregivers felt generally positive about the tDCS intervention. To patients, it appealed that the tDCS intervention offered something extra in addition to their regular therapy; they were motivated to do as much as possible to recover from their symptoms.

> *["My motivation was mainly: There is no pain in trying. If it is placebo, it does no harm, and if it is not the placebo then it might, well, give me positive effects."]* **P5**

Some patients additionally expressed a specific interest in the technological or brain-focused working mechanisms of tDCS, or just wanted to help developing new treatment options. Most caregivers expressed a similar interest, especially towards the cognitive and neurobiological targets of the treatment. Moreover, caregivers recognized that, beside their interest, one of the main reasons for their patients to participate was their desperation to take on 'any' treatment available. As a patient stated:

> *["I mean I was very much in need of help. I was a bit desperate, and I thought, you know, I do whatever it takes."]* **P7**

Some respondents expressed a negative attitude to specific aspects of the intervention. Two patients thought the treatment setting had a 'low budget' appearance, mainly due to the look of tDCS equipment (e.g., simple rubber band straps around the head), and to the relatively small, non-modern test room. On the other hand, two other patients specifically mentioned to be content with the treatment setting and the quiet test room. Also, some patients felt unsafe about the treatment before starting the tDCS intervention. A patient expressed this feeling as:

> *["It's the idea, you know…you're getting shocks in your head. They are playing with your head."]* **P3**

Some caregivers pointed out that patients suffering from stress-related disorders are more prone to feelings of unsafety and suspicion, and pointed out that such feelings may pose a barrier to adhering to a tDCS treatment.

ii) **Burden**

Respondents initially deemed the overall burden of the tDCS intervention low. On a physical level, patients indicated that tDCS associated sensations were tolerated well. Only two patients mentioned a mild burden of headaches or burning and itching sensations after the sessions. On a psychological level, the tDCS sessions were experienced as relatively easy, although the cognitive task during the tDCS sessions was experienced as monotonous and long. Furthermore, the novel and unfamiliar nature of the intervention made a patient feel ill at ease:

> *["When you sit down there, you feel more tense. Then you get the, uhm, current. And you do feel that, yes you do. (…) At a certain moment I felt at ease. But the first few times I didn't. Then you feel a bit... See, it is all new."]* **P1**

On a practical level, both patients and caregivers pointed out that a 5-session tDCS intervention is a low burden, especially when compared to regular treatment schemes. However, for some patients traveling towards the hospital posed a high burden, as traveling caused them a lot of anxiety and stress. Also patients with a short travel time declared that a longer travel time

would cause a higher burden. Caregivers indeed pointed out that for patients with stress-related disorders travel time should be as short as possible. One patient explained:

> *["I got very aggressive in traffic. (…) And the train is even worse. There, people don't do what you want. So, transport from A to B in a crowded space is quite a problem."]* **P6**

He later added:

> *["But you can't send it [the tDCS equipment] home as a package and say: Here you are, do this."]* **P6**

Furthermore, one patient suggested to offer tDCS participants some time to 'recover' after each tDCS session, to relieve the potential tension caused by the session and to feel more secure to travel home.

iii) **Opportunity costs**

The opportunity costs of the tDCS intervention were deemed low by all respondents. Because all patients were allowed time off from work for treatment, patients didn't perceive that the time invested in participation posed opportunity costs at the moment, but most of them anticipated higher costs with heavier intervention schemes or full-time job obligations. In addition, some caregivers noted the potential difficulty in treatment adherence in this specific population due to military training and operations abroad.

iv) **Ethicality**

Patients particularly appreciated that the tDCS intervention did not trigger negative thoughts or fearful memories, in contrary to the exposure in psychotherapy. For some patients, the tDCS sessions even offered distraction from negative thoughts or anxious feelings. Some patients therefore ascribed a high ethicality value to the tDCS intervention, and would favor tDCS over psychotherapy if a tDCS treatment would be equally effective. As one patient noted:

> *["You don't have to put everything on the table, you don't have to dig stuff up. It is fast and comfortable."]* **P6**

However, at the same time, both patients and caregivers expressed the expectation that tDCS would only 'work' in combination with psychotherapy. All respondents deemed it necessary for recovery to talk about their mental health problems and the underlying causes. One patient also mentioned he missed social therapeutic interaction during the intervention.

A second theme that emerged from the caregivers' perspective is the particular suitability of tDCS treatments for military personnel because of its 'high-tech' feel, which may lower the barrier to treatment:

> *["The association with cyber, space, earplugs. I think that [the technology] is a benefit for this subpopulation."]* **CG2**

v) **Perceived effectiveness**

Most patients perceived no significant effect of tDCS on their symptoms. Because all patients received psychological or pharmacological treatment in parallel, patients who reported improvements in mental health after the tDCS intervention could not specifically attribute this to tDCS.

Caregivers acknowledged a potential of the technology as add-on to existing treatments for this patient group. However, caregivers in general did not expect tDCS effects to be 'ground-breaking', especially not when stress-related symptoms are caused by more complex underlying issues, e.g., related to childhood trauma or personality.

Some patients did report short-term improvements in their ability to focus, cognitive 'clarity', or a generally calmer mood. These short-term effects disappeared directly after the tDCS session or in the days afterwards.

vi) **Coherence**

Most patients and caregivers felt they were adequately informed about the tDCS intervention:

> *["It was all explained to me quite well. And you do a test beforehand [an impulse control task], and then you know what to expect. In practice, it's more or less the same."]* **P2**

> *["And [the researcher] took a lot of effort to explain it."]* **CG1**

In sharp contrast, however, all patients and most caregivers expressed a lack of sufficient understanding of the tDCS intervention. The same caregiver (CG1), for example, continued to say:

> *["And then you think: I remember so little of it. I just find it a bit shocking how little I know about it."]* **CG1**

A patient mentioned:

> *["I don't know how it works. The only thing I know is that they gave me a screen, and I had to push buttons."]* **P3**

(Pushing buttons refers to the cognitive task during the tDCS sessions.)The majority of respondents reported a general feeling of incomprehension towards the clinical mechanism of action; the relationship between the tDCS intervention and the disorder-specific symptoms was unclear to most respondents. As one patient put it:

> *["Then [after the first tDCS session] I thought: Well, I'm not sure if this is going to help me deal with the problem."]* **P4**

A number of caregivers and patients pointed out that the neurobiological working mechanisms of tDCS were hard to grasp for them.

In response to this treatment incomprehension, a second theme emerged, comprising the importance of treatment coherence. According to the patients, better comprehension of how tDCS works and how tDCS can affect their symptoms is critical because it would (i) reduce feelings of stress resulting from not knowing what effects to expect, (ii) improve their personal contribution to facilitate the treatment's effects, and (iii) increase motivation to adhere to the treatment. One caregiver elucidated why treatment coherence is especially important for patients with stress-related disorders:

> *[Very important. It can be a vehicle for participating in a state-of-the-art treatment. Because then, they can trust it. And only then they can 'surrender' to treatment.']* **CG3**

Another caregiver conceived it critical that caregivers should fully understand the treatment's mechanism of action, also because the patient's decision to participate in a novel healthcare intervention often depends on the opinion of the caregiver.

Two patients suggested to explain the working mechanisms of tDCS in a simpler manner and making use of 'imagery'.

vii) **Self-efficacy**

Patients overall felt capable to adhere to all of the intervention components. Caregivers did also not foresee capability problems associated with the tDCS intervention.

Yet, although not directly related to tDCS, two patients reported the inability to maintain focus during the cognitive task, and two patients encountered difficulty in comprehending the written information and questionnaire items.

DISCUSSION

The acceptability of novel treatments such as tDCS contributes significantly to its successful implementation in clinical practice. If tDCS is to play an important role in treating stress-related disorders, its acceptability in this context is important to understand. This mixed methods study is the first to examine the acceptability of tDCS as a treatment tool for stress-related mental health disorders from both the patient and caregiver perspective. We gathered quantitative measures of acceptability in an RCT with 102 military patients undergoing a 5-session tDCS intervention, including the dropout rate, adverse side effects and emotional responses to the tDCS sessions. In an additional exploratory study, we carried out semi-structured interviews based on the TFA[33] to gather in-depth information on the full range of views and experiences with tDCS among a subgroup of the patients and a group of caregivers.

In summary, the quantitative outcomes showed relatively high acceptability of tDCS; treatment adherence was high and only mild adverse sensations on the scalp could be directly attributed to tDCS, conform recently updated tDCS adverse effects profiles[42]. This was supported by the qualitative outcomes, showing that the affective attitude towards the tDCS intervention was predominantly positive. Also, the burden and opportunity costs were deemed low and self-efficacy was high. Regarding ethicality, tDCS fitted well into the value system of the respondents, although the technique was mainly perceived as complementary to psychotherapy. Strikingly, however, the tDCS intervention coherence was very limited among patients as well as caregivers. Furthermore, the applied short tDCS intervention was not perceived as effective to treat the stress-related symptoms. A higher travel barrier was anticipated for more intensive treatment schemes. Below, we further discuss the major findings.

The most notable finding was the mismatch in perspectives on treatment coherence. Although patients and caregivers expressed their impression that sufficient explanation of the study and intervention had been provided, almost all respondents showed limited comprehension of the clinical mechanisms of action of tDCS. This may be related to unfamiliarity with the neurobiological processes targeted by tDCS. Patients and caregivers both emphasized the importance of understanding the working mechanisms of a tDCS intervention and its intended impact on clinically relevant outcomes. Respondents anticipated that better understanding could improve the affective attitude towards the technique, lower the barrier to participate and increase treatment adherence. Low treatment coherence also seemed to negatively impact the ethicality, as some patients expressed that they didn't know how the tDCS intervention would 'help them'. A negative impact of low treatment coherence on other acceptability aspects is consistent with previous findings. For example, limited understanding of psychotherapy processes also induces skepticism towards the treatment among patients and caregivers[43,44]. User's expectations may also directly influence tDCS effectiveness[45]. Appropriately educating users on tDCS thus appears vital for its acceptability and effectivity as a treatment tool.

This likely also applies to brain stimulation tools like TMS and other novel (neurobiological) treatment options.

Respondents found no significant burden or opportunity costs in a tDCS intervention. Contrary to previous findings[25], our patients perceived only mild adverse side effects of tDCS and did not experience tDCS sensations as a burden or barrier. Interestingly, besides the itching or burning sensations on the scalp, most adverse effects could not directly be attributed to active tDCS, suggesting that such adverse effects (e.g., head ache) are linked to general RCT participation rather than to active tDCS itself. However, a potential burden was perceived in travelling towards the hospital for the tDCS sessions; travelling can be a severe trouble for patients with stress-related disorders, and specifically for this population also during military training or operational activities abroad. Veterans with PTSD in general seem to regard frequent visits as a disadvantage of treatment[46]. To lower the travel barrier, taking more advantage of the technique's portability and further developing home-based tDCS is highly recommended. Despite some obstacles (e.g. adverse effects due to misuse[47–49]), the feasibility of home-based tDCS is already increasing[50,51]. Also, home-based tDCS may have additional potential to treatment in the post COVID-19 era.

Regarding the ethicality of the tDCS intervention, patients and caregivers were positive for different reasons. The caregivers expected that the intervention's 'technological feel' could appeal to military patients and thereby lower treatment barriers. Indeed, incorporating technological methods that appeal to a population may be beneficial for psychiatric treatment[52]. Instead, the patients particularly appreciated the low emotional burden of the tDCS intervention, i.e., the possibility of treatment without exposure to trauma or feared situations. Correspondingly, less focus on verbal communication and lower perceived stress during treatment sessions are also particularly appreciated aspects in EMDR therapy for stress-related disorders[44,46], while trauma exposure is experienced as a struggle in regular psychotherapy[43,53]. For military PTSD patients, exposure to trauma during therapy even poses a major barrier to psychotherapeutic treatment[54]. On the other hand, patients were also uncertain about how well the tDCS intervention could address their symptoms. Neither patients nor caregivers believed that a technique like tDCS can completely replace psychotherapy or 'talking'. In fact, 'talking', personal contact and the role of the caregiver are regarded as the most important aspects of psychotherapy[44] that positively contribute to willingness to participate in research (especially among traumatized patients[55]), treatment acceptability[53,56], therapeutic effectivity, and self-efficacy in managing symptoms[43,53,56–59]. Accordingly, treatments for PTSD and anxiety without these interpersonal aspects (e.g. medication) are commonly prescribed only as add-on to psychotherapy[60]. Taken together, the technical feel and minimal emotional burden of a tDCS intervention might be useful to lower the barrier to seek treatment, but our findings suggest that tDCS for stress-related disorders should ultimately be offered in addition to an interpersonal treatment option like psychotherapy.

Furthermore, the respondents' positive attitude towards participating in the intervention stemmed mainly from a general motivation to explore alternative treatment options. Hope for recovery and desire for treatment innovation were also the main reasons for tDCS participation in a previous study[28]. Notably, the characteristics of the equipment and treatment setting had a significant influence on patients' affective attitude, either in a positive or negative way. The technique also induced some initial feelings of unsafety among patients. As also pointed out by the caregivers, patients with stress-related disorder are prone to anxious feelings prior to starting a novel treatment[43,53,56,58] and may prefer treatments they are familiar with[46]. To improve the affective attitude towards tDCS as a professional treatment tool, attention should be paid to the appearance and comfort of the equipment and treatment setting, and to patients' understanding of the treatment and its safety profile.

Finally, patients expressed the feeling that many more tDCS sessions would be needed in order to effectuate a clinically significant change. The perceived clinical effects of this short tDCS intervention on symptoms were very limited or completely absent. Yet, in line with previously reported experiences with tDCS[26,28], patients perceived increased focus and cognitive 'clarity' during tDCS or in the hours afterwards.

STUDY STRENGTHS AND LIMITATIONS

This study extended knowledge on tDCS acceptability to the context of stress-related disorders, military patients and, importantly, to the level of the caregiver. Furthermore, the relevance and reliability of our findings were maximized by combining quantitative data with qualitative outcomes in a mixed methods approach, and by using a validated theoretical framework and analysis method for the qualitative data. We therefore believe that these results make an important contribution to insights in the acceptability of tDCS in mental health care.

Yet, our study met a number of limitations. First, we investigated a sample of military and mainly male respondents. All respondents were also individuals who voluntarily participated in an RCT. Our results may represent the specific views of this population, although we believe that the most important findings are generalizable to other patients with stress-related disorders (e.g., regarding the difficulty comprehending tDCS working mechanisms and the travel burden). Second, no new themes emerged in the last interviews, indicating that the most important themes are covered by the data. However, the sample size of the interview study was relatively low, especially compared to the sample size of the quantitative study. Future studies are needed to confirm our qualitative findings in larger samples and other populations. Third, it should be mentioned that our findings are closely connected with the characteristics of the tDCS intervention as applied in our study. For example, the cognitive training on the stop-signal task should be seen as part of the total experience of the tDCS intervention. This may have influenced the experience with tDCS itself. Likewise, some of our findings may be very study-specific, such as aspects of the affective attitude (e.g., regarding tDCS equipment) and perceived effectiveness, which can limit the generalizability of our findings towards other

types of tDCS interventions. It should also be noted that the quantitative measures were taken during the tDCS intervention, while the interviews were conducted one or more months after tDCS participation. Although respondents did generally not report to have large issues with remembering specific details of the tDCS intervention, the qualitative data depended on the accuracy of the participants' memory recall. In this respect, there is a discrepancy between the quantitative and qualitative data; the numbers reflect immediate tDCS experiences, while the interview results reflect overarching retrospective perspectives on tDCS as a technique for stress-related disorder treatment.

CONCLUSION

In this study we investigated the acceptability of tDCS for the first time in the context of stress-related disorder treatment. High treatment adherence and minimal adverse side effects reflected high acceptability of tDCS. Exploratory findings on the subjective perspectives of military patients and their professional caregivers also showed that tDCS is overall regarded as an acceptable complementary treatment tool for stress-related disorders. However, our respondents raised two major issues. First, limited understanding of how tDCS works as a treatment tool highlighted the need to improve treatment comprehension. The essence of treatment comprehension was further emphasized by its negative influence on the affective attitude and perceived suitability of tDCS to treat stress-related symptoms. Second, travelling for treatment visits potentially poses an important barrier in this population. This barrier will grow when more (frequent) sessions are required for clinical effectiveness. Although the results reported here are closely connected with the way tDCS was applied in our study, they highlight that efforts should be made to better educate tDCS users and further develop home-based tDCS solutions to secure optimal tDCS acceptability and, in turn, intervention success.

LIST OF ABBREVIATIONS

CBT = cognitive behavioral therapy
EMDR = eye movement desensitization and reprocessing
PTSD = posttraumatic stress disorder
RCT = randomized-controlled trial
STAI-6 = six-item short-form of the State-Trait Anxiety Inventory
tDCS = transcranial direct current stimulation
TFA = theoretical framework of acceptability
TMS = transcranial magnetic stimulation

DECLARATIONS

Ethics approval and consent to participate

The RCT and the interview study were both approved by the Ethics Committee of the University Medical Center Utrecht, and carried out in accordance with declaration of Helsinki. All patients gave written informed consent for participation in the RCT after receiving written and verbal

explanation of the RCT. All interview respondents additionally provided written informed consent before the start of the interview.

Consent to publish

Not applicable.

Availability of data and materials

All quantitative data analyzed during this study are included in this published article and its Appendix.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

FS designed the study (RCT and interview study), collected and analyzed the quantitative data (RCT), and wrote the manuscript. GK designed the study (interview study), collected and analyzed the qualitative data (interview study) and was a major contributor to writing the manuscript. EG designed the study (RCT and interview study), and revised the manuscript. All authors read and approved the final version of the manuscript.

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REFERENCES

1. Bradley R, Greene J, Russ E, Dutra L, Westen D. A Multidimensional Meta-Analysis of Psychotherapy for PTSD. *American Journal of Psychiatry*. 2005;162(2):214-227. doi:10.1176/appi.ajp.162.2.214

2. Spinhoven P, Batelaan N, Rhebergen D, van Balkom A, Schoevers R, Penninx BW. Prediction of 6-yr symptom course trajectories of anxiety disorders by diagnostic, clinical and psychological variables. *Journal of Anxiety Disorders*. 2016;44:92-101. doi:10.1016/j.janxdis.2016.10.011

3. Sripada RK, Blow FC, Rauch SAM, et al. Examining the nonresponse phenomenon: Factors associated with treatment response in a national sample of veterans undergoing residential PTSD treatment. *Journal of Anxiety Disorders*. 2019;63:18-25. doi:10.1016/j.janxdis.2019.02.001

4. Resick PA, Wachen JS, Dondanville KA, et al. Effect of Group vs Individual Cognitive Processing Therapy in Active-Duty Military Seeking Treatment for Posttraumatic Stress Disorder. *JAMA Psychiatry*. 2017;74(1):28. doi:10.1001/jamapsychiatry.2016.2729

5. van Rooij SJ, Geuze E, Kennis M, Rademaker AR, Vink M. Neural Correlates of Inhibition and Contextual Cue Processing Related to Treatment Response in PTSD. *Neuropsychopharmacology*. 2015;40(3):667-675. doi:10.1038/npp.2014.220

6. Brunoni AR, Nitsche MA, Bolognini N, et al. Clinical research with transcranial direct current stimulation (tDCS): Challenges and future directions. *Brain Stimulation*. 2012;5(3):175-195. doi:10.1016/j.brs.2011.03.002

7. Priori A, Hallett M, Rothwell JC. Repetitive transcranial magnetic stimulation or transcranial direct current stimulation? *Brain Stimulation*. 2009;2(4):241-245. doi:10.1016/j.brs.2009.02.004

8. Vicario CM, Salehinejad MA, Felmingham K, Martino G, Nitsche MA. A systematic review on the therapeutic effectiveness of non-invasive brain stimulation for the treatment of anxiety disorders. *Neuroscience and Biobehavioral Reviews*. 2019;96(August 2018):219-231. doi:10.1016/j.neubiorev.2018.12.012

9. Marin MF, Camprodon J a., Dougherty DD, Milad MR. Device-based brain stimulation to augment fear extinction: Implications for ptsd treatment and beyond. *Depression and Anxiety*. 2014;31(4):269-278. doi:10.1002/da.22252

10. Kadam UT, Croft P, McLeod J, Hutchinson M. A qualitative study of patients' views on anxiety and depression. *British Journal of General Practice*. 2001;51(466):375-380.

11. Wagner AW, Bystritsky A, Russo JE, et al. Beliefs about psychotropic medication and psychotherapy among primary care patients with anxiety disorders. *Depression and Anxiety*. 2005;21(3):99-105. doi:10.1002/da.20067

12. Alfonsson S, Olsson E, Hursti T. Motivation and Treatment Credibility Predicts Dropout, Treatment Adherence, and Clinical Outcomes in an Internet-Based Cognitive Behavioral Relaxation Program: A Randomized Controlled Trial. *Journal of Medical Internet Research*. 2016;18(3):e52. doi:10.2196/jmir.5352

13. Finch J, Ford C, Grainger L, Meiser-Stedman R. A systematic review of the clinician related barriers and facilitators to the use of evidence-informed interventions for post traumatic stress. *Journal of Affective Disorders*. 2020;263:175-186. doi:10.1016/j.jad.2019.11.143

14. Knotkova H, Nitsche MA, Bikson M, Woods AJ, eds. *Practical Guide to Transcranial Direct Current Stimulation*. Springer International Publishing; 2019. doi:10.1007/978-3-319-95948-1

15. Tortella G, Casati R, Aparicio LVM, et al. Transcranial direct current stimulation in psychiatric disorders. *World Journal of Psychiatry*. 2015;5(1):88. doi:10.5498/wjp.v5.i1.88

16. Kuo MF, Paulus W, Nitsche MA. Therapeutic effects of non-invasive brain stimulation with direct currents (tDCS) in neuropsychiatric diseases. *NeuroImage*. 2014;85:948-960. doi:10.1016/j.neuroimage.2013.05.117

17. Brunoni AR, Palm U. Transcranial Direct Current Stimulation in Psychiatry: Mood Disorders, Schizophrenia and Other Psychiatric Diseases. In: *Practical Guide to Transcranial Direct Current Stimulation*. Springer, Cham.; 2019:431-471.

18. Brunoni AR, Amadera J, Berbel B, Volz MS, Rizzerio BG, Fregni F. A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. *The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum (CINP)*. 2011;14(8):1133-1145. doi:10.1017/S1461145710001690

19. Aparício LVM, Guarienti F, Razza LB, Carvalho AF, Fregni F, Brunoni AR. A Systematic Review on the Acceptability and Tolerability of Transcranial Direct Current Stimulation Treatment in Neuropsychiatry Trials. *Brain Stimulation*. 2016;9(5):671-681. doi:10.1016/j.brs.2016.05.004

20. Moffa AH, Brunoni AR, Fregni F, et al. Safety and acceptability of transcranial direct current stimulation for the acute treatment of major depressive episodes: Analysis of individual patient data. *Journal of Affective Disorders*. 2017;221:1-5. doi:10.1016/j.jad.2017.06.021

21. Schottenbauer MA, Glass CR, Arnkoff DB, Tendick V, Gray SH. Nonresponse and Dropout Rates in Outcome Studies on PTSD: Review and Methodological Considerations. *Psychiatry: Interpersonal and Biological Processes*. 2008;71(2):134-168. doi:10.1521/psyc.2008.71.2.134

22. Imel ZE, Laska K, Jakupcak M, Simpson TL. Meta-analysis of dropout in treatments for posttraumatic stress disorder. *Journal of Consulting and Clinical Psychology*. 2013;81(3):394-404. doi:10.1037/a0031474

23. d'Ardenne P, Heke S. Patient-reported outcomes in post-traumatic stress disorder part I: Focus on psychological treatment. *Dialogues in Clinical Neuroscience*. 2014;16(2):213-226.

24. Gersh E, Hallford DJ, Rice SM, et al. Systematic review and meta-analysis of dropout rates in individual psychotherapy for generalized anxiety disorder. *Journal of Anxiety Disorders*. 2017;52:25-33. doi:10.1016/j.janxdis.2017.10.001

25. Tedesco Triccas L, Burridge JH, Hughes AM, et al. A qualitative study exploring views and experiences of people with stroke undergoing transcranial direct current stimulation and upper limb robot therapy. *Topics in Stroke Rehabilitation*. 2018;25(7):480-488. doi:10.1080/10749357.2018.1493072

26. Knotkova H, Rosedale M, Strauss SM, et al. Using Transcranial Direct Current Stimulation to Treat Depression in HIV-Infected Persons: The Outcomes of a Feasibility Study. *Frontiers in Psychiatry*. 2012;3. doi:10.3389/fpsyt.2012.00059

27. Ownby R, Acevedo A. A pilot study of cognitive training with and without transcranial direct current stimulation to improve cognition in older persons with HIV-related cognitive impairment. *Neuropsychiatric Disease and Treatment*. 2016;12:2745-2754. doi:10.2147/NDT.S120282

28. Danzl MM, Chelette KC, Lee K, Lykins D, Sawaki L. Brain stimulation paired with novel locomotor training with robotic gait orthosis in chronic stroke: A feasibility study. Krebs HI, ed. *NeuroRehabilitation*. 2013;33(1):67-76. doi:10.3233/NRE-130929

29. Poreisz C, Boros K, Antal A, Paulus W. Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. *Brain Research Bulletin*. 2007;72(4-6):208-214. doi:10.1016/j.brainresbull.2007.01.004

30. Sekhon M, Cartwright M, Francis JJ. Acceptability of healthcare interventions: an overview of reviews and development of a theoretical framework. *BMC Health Services Research*. 2017;17(1):88. doi:10.1186/s12913-017-2031-8

31. O'Cathain A, Hoddinott P, Lewin S, et al. Maximising the impact of qualitative research in feasibility studies for randomised controlled trials: guidance for researchers. *Pilot and Feasibility Studies*. 2015;1(1):32. doi:10.1186/s40814-015-0026-y

32. Lewin S, Glenton C, Oxman AD. Use of qualitative methods alongside randomised controlled trials of complex healthcare interventions: methodological study. *BMJ*. 2009;339(sep10 1):b3496-b3496. doi:10.1136/bmj.b3496

33. Sekhon M, Cartwright M, Francis JJ. Acceptability of health care interventions: A theoretical framework and proposed research agenda. *British Journal of Health Psychology*. 2018;23(3):519-531. doi:10.1111/bjhp.12295

34. Sekhon M, Cartwright M, Francis JJ. Acceptability of healthcare interventions: an overview of reviews and development of a theoretical framework. *BMC Health Services Research*. 2017;17(1):88. doi:10.1186/s12913-017-2031-8

35. Pluye P, Hong QN. Combining the Power of Stories and the Power of Numbers: Mixed Methods Research and Mixed Studies Reviews. *Annual Review of Public Health*. 2014;35(1):29-45. doi:10.1146/annurev-publhealth-032013-182440

36. Logan GD, Cowan WB, Davis KA. On the ability to inhibit simple and choice reaction time responses: A model and a method. *Journal of Experimental Psychology: Human Perception and Performance*. 1984;10(2):276-291. doi:10.1037/0096-1523.10.2.276

37. Aupperle RL, Melrose AJ, Stein MB, Paulus MP. Executive function and PTSD: Disengaging from trauma. *Neuropharmacology*. 2012;62(2):686-694. doi:10.1016/j.neuropharm.2011.02.008

38. van Rooij SJH, Jovanovic T. Impaired inhibition as an intermediate phenotype for PTSD risk and treatment response. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2019;89:435-445. doi:10.1016/j.pnpbp.2018.10.014

39. Marteau TM, Bekker H. The development of a 6-item short-form of the state scale of the Spielberger State Trait Anxiety Inventory (STAI). *British Journal of Clinical Psychology*. 1992;31:301-306.

40. Gale NK, Heath G, Cameron E, Rashid S, Redwood S. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. *BMC Medical Research Methodology*. 2013;13(1):117. doi:10.1186/1471-2288-13-117

41. Elo S, Kyngäs H. The qualitative content analysis process. *Journal of Advanced Nursing*. 2008;62(1):107-115. doi:10.1111/j.1365-2648.2007.04569.x

42. Nikolin S, Huggins C, Martin D, Alonzo A, Loo CK. Safety of repeated sessions of transcranial direct current stimulation: A systematic review. *Brain Stimulation*. 2018;11(2):278-288. doi:10.1016/j.brs.2017.10.020

43. Shearing V, Lee D, Clohessy S. How do clients experience reliving as part of trauma-focused cognitive behavioural therapy for posttraumatic stress disorder? *Psychology and Psychotherapy: Theory, Research and Practice*. 2011;84(4):458-475. doi:10.1111/j.2044-8341.2010.02012.x

44. Unwin G, Willott S, Hendrickson S, Stenfert Kroese B. Eye movement desensitization and reprocessing for adults with intellectual disabilities: Process issues from an acceptability study. *Journal of Applied Research in Intellectual Disabilities*. 2019;32(3):635-647. doi:10.1111/jar.12557

45. Rabipour S, Wu AD, Davidson PSR, Iacoboni M. Expectations may influence the effects of transcranial direct current stimulation. *Neuropsychologia*. 2018;119:524-534. doi:10.1016/j.neuropsychologia.2018.09.005

46. Etingen B, Grubbs KM, Harik JM. Drivers of Preference for Evidence-Based PTSD Treatment: A Qualitative Assessment. *Military Medicine*. 2020;185(Supplement_1):303-310. doi:10.1093/milmed/usz220

47. Lefaucheur JP, Antal A, Ayache SS, et al. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). *Clinical Neurophysiology*. 2017;128(1):56-92. doi:10.1016/j.clinph.2016.10.087

48. Antal A, Woods AJ, Knotkova H. Transcranial Direct Current Stimulation Ethics and Professional Conduct. In: *Practical Guide to Transcranial Direct Current Stimulation*. Springer International Publishing; 2019:407-427. doi:10.1007/978-3-319-95948-1_14

49. Palm U, Kumpf U, Behler N, et al. Home Use, Remotely Supervised, and Remotely Controlled Transcranial Direct Current Stimulation: A Systematic Review of the Available Evidence. *Neuromodulation: Technology at the Neural Interface*. 2018;21(4):323-333. doi:10.1111/ner.12686

50. Hordacre B. The Role of Telehealth to Assist In-Home tDCS: Opportunities, Promising Results and Acceptability. *Brain Sciences*. 2018;8(6):102. doi:10.3390/brainsci8060102

51. Alonzo A, Fong J, Ball N, Martin D, Chand N, Loo C. Pilot trial of home-administered transcranial direct current stimulation for the treatment of depression. *Journal of Affective Disorders*. Published online 2019. doi:10.1016/j.jad.2019.04.041

52. Orengo-Aguayo RE, Hanson RF, Moreland AD, Jobe-Shields L, Adams ZW. Enhancing the Delivery of an Empirically-Supported Trauma-Focused Treatment for Adolescents: Providers' Views of the Role of Technology and Web-Based Resources. *Administration and Policy in Mental Health and Mental Health Services Research*. 2018;45(4):575-586. doi:10.1007/s10488-017-0846-6

53. Vincent F, Jenkins H, Larkin M, Clohessy S. Asylum-Seekers' Experiences of Trauma-Focused Cognitive Behaviour Therapy for Post-Traumatic Stress Disorder: A Qualitative Study. *Behavioural and Cognitive Psychotherapy*. 2013;41(5):579-593. doi:10.1017/S1352465812000550

54. Sayer NA, Friedemann-Sanchez G, Spoont M, et al. A Qualitative Study of Determinants of PTSD Treatment Initiation in Veterans. *Psychiatry: Interpersonal and Biological Processes*. 2009;72(3):238-255. doi:10.1521/psyc.2009.72.3.238

55. Schwerdtfeger KL. The Appraisal of Quantitative and Qualitative Trauma-Focused Research Procedures among Pregnant Participants. *Journal of Empirical Research on Human Research Ethics*. 2009;4(4):39-51. doi:10.1525/jer.2009.4.4.39

56. Karatzias T, Brown M, Taggart L, et al. A mixed-methods, randomized controlled feasibility trial of Eye Movement Desensitization and Reprocessing (EMDR) plus Standard Care (SC) versus SC alone for DSM-5 Posttraumatic Stress Disorder (PTSD) in adults with intellectual disabilities. *Journal of Applied Research in Intellectual Disabilities*. 2019;32(4):806-818. doi:10.1111/jar.12570

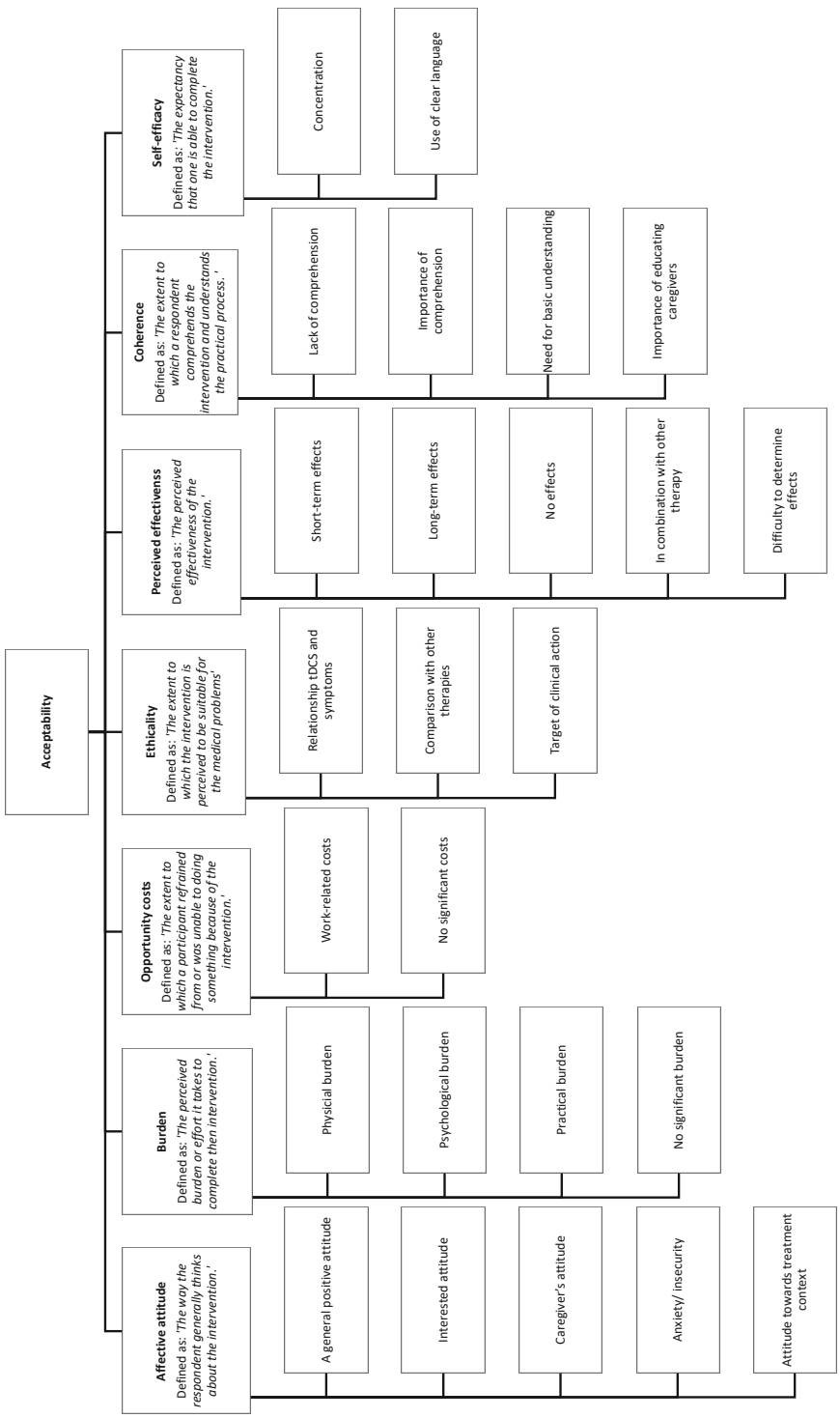
57. Cotter P, Meysner L, Lee CW. Participant experiences of Eye Movement Desensitisation and Reprocessing vs. Cognitive Behavioural Therapy for grief: similarities and differences. *European Journal of Psychotraumatology*. 2017;8(sup6):1375838. doi:10.1080/20008198.2017.1375838

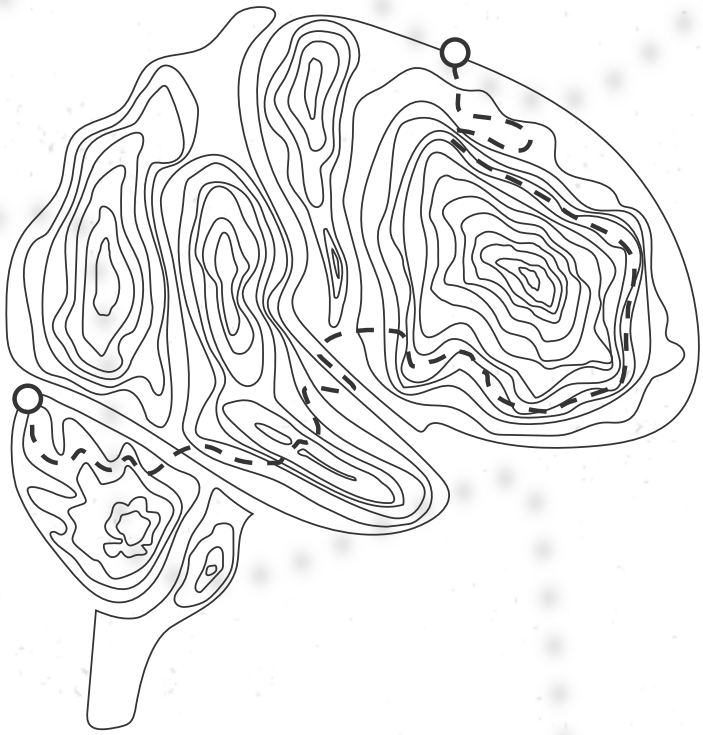
58. Neelakantan L, Hetrick S, Michelson D. Users' experiences of trauma-focused cognitive behavioural therapy for children and adolescents: a systematic review and metasynthesis of qualitative research. *European Child & Adolescent Psychiatry*. 2019;28(7):877-897. doi:10.1007/s00787-018-1150-z

59. Lambert MJ, Barley DE. Research summary on the therapeutic relationship and psychotherapy outcome. *Psychotherapy: Theory, Research, Practice, Training*. 2001;38(4):357-361. doi:10.1037/0033-3204.38.4.357

60. Kapfhamme HP. Patient-reported outcomes in post-traumatic stress disorder Part II: Focus on pharmacological treatment. *Dialogues in Clinical Neuroscience*. 2014;16(2):227-237.

Appendix: Final coding scheme.





CHAPTER 5

Effects of multisession transcranial direct current stimulation on stress regulation and emotional working memory: a randomized controlled trial in healthy military personnel

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ABSTRACT

Objectives: Top-down stress regulation, important for military operational performance and mental health, involves emotional working memory and the dorsolateral prefrontal cortex (DLPFC). Multisession transcranial direct current stimulation (tDCS) over the DLPFC during working memory training has been shown to improve working memory performance. The present study tested the hypothesis that combined tDCS with working memory training also improves top-down stress regulation. However, tDCS-response differs between individuals. Resting-state electrophysiological brain activity was post-hoc explored as a possible predictor of tDCS-response. The predictive value of the ratio between slow-wave theta oscillations and fast-wave beta oscillations (theta/beta ratio) was examined, together with the previously identified tDCS-response predictors age, education and baseline working memory performance.

Materials and Methods: Healthy military servicemembers (n=79) underwent three sessions of real or sham tDCS over the right DLPFC (anode: F4, cathode: behind C2) at 2 mA for 20 minutes during emotional working memory training (*N*-Back task). At baseline and within a week after the tDCS-training sessions, stress regulation was assessed by fear-potentiated startle responses and subjective fear in a threat-of-shock paradigm with instructed emotional downregulation. Results were analyzed in generalized linear mixed-effects models.

Results: Threat-of-shock responses and emotional working memory performance showed no significant group-level effects of the real versus sham tDCS-training intervention ($p>.07$). In contrast, when taking into account baseline theta/beta ratios or the other tDCS-response predictors, exploratory results showed a trait-dependent beneficial effect of tDCS on emotional working memory training performance during the first session ($p<.01$).

Conclusions: No evidence was found for effectivity of the tDCS-training intervention to improve stress regulation in healthy military personnel. The emotional working memory training results emphasize the importance of studying effects of tDCS in relation to individual differences.

INTRODUCTION

Military personnel risk exposure to a variety of stressors, including physical danger and witnessing severe human suffering[1,2]. Prolonged and high levels of stress can impair operational performance[3] and contribute to the development of mental health problems like anxiety and posttraumatic stress disorder (PTSD)[4,5]. Adequate top-down regulation of stress-related reactions and emotions contributes to psychological resilience against these adverse effects of stress[6–10]. Cognitive strategies for top-down stress regulation involve, for instance, re-evaluating the value or meaning of a stressful situation to reduce its emotional impact[11].

However, the effectiveness of top-down stress regulation may be compromised when stress levels are too high[12]. Both acute and chronic stress levels interfere with functioning of the prefrontal cortex, especially in the dorsolateral parts (DLPFC) that play a substantial role in stress regulation[13,14] and cognitive functions like working memory[15]. Instead, better stress regulation has been associated with better working memory performance, specifically in the emotional domain[16–19]. Emotional working memory plays a role by actively keeping threat-related information available and allowing for selecting and updating this information to deploy effective stress regulation strategies[20]. Accordingly, the right DLPFC has been identified as a target region for non-invasive brain stimulation to improve symptoms of stress-related disorders, including PTSD[21]. Also in healthy volunteers, several studies demonstrated that stress regulation improved after applying transcranial direct current stimulation (tDCS) over the right DLPFC or the neighboring ventrolateral PFC[22–27].

TDCS modulates subthreshold cortical excitability and plasticity by polarizing nerve tissue using low intensity electrical currents (1-2.5 mA) administered over the scalp. Cortical excitability is generally assumed to increase by anodal tDCS and decrease by cathodal tDCS, although the exact mechanisms underlying tDCS effects are still unclear (for further reading see[28,29]). Single-session tDCS, however, yields transient neurophysiological effects that typically fade out within a few hours[30], and single-session tDCS over the DLPFC does not always effectively modulate stress regulation[31–33].

More consistent and sustained effects on higher-order cognitive functions and on symptoms of depression and PTSD are suggested to follow from multiple sessions of tDCS over the DLPFC or the ventrolateral PFC, particularly when applied during a neurocognitive training or therapy that activates the tDCS-targeted brain region[34–41]. One way to activate the right DLPFC is by a working memory task that is shown to activate several PFC regions involved in stress regulation[18,42]. The idea that working memory performance can be improved by anodal tDCS over the DLPFC is supported by converging evidence from a recent meta-analysis[43]. Additionally, several studies suggest that multisession tDCS during working memory training may lead to long-lasting performance gains in working memory and other cognitive functions depending on working memory[44–47], indicating a potential benefit for stress regulation capacity.

However, not all studies of combined tDCS with working memory training find these beneficial effects, see for example[48,49]. These negative findings could be related to the considerable variability between individuals in tDCS-effects on cognitive functions like working memory[37,50]. This variability has been associated with factors like age[51–53], baseline cognitive performance[54–58] and education[59]. Variability in tDCS-response may be even better explained by neural processes that interact with tDCS, such as indicated by markers from electroencephalography (EEG)[60–62]. One EEG marker that could be related to tDCS-effects on emotional working memory is the power ratio between slow-wave theta band activity (4-7 Hz) and fast-wave beta band activity (13-30 Hz) in resting-state EEG, i.e., the theta/beta ratio[63–65]. The theta/beta ratio is thought to reflect the balance between subcortical-based emotional and motivational drives and cortical-based cognitive control, as it has been associated with cognitive control over emotional input[66–68], reward-motivated learning on cognitive tasks[69–71] and working memory training gains[72]. The theta/beta ratio was previously also associated with cognitive effects of a tDCS-related technique, transcranial random noise stimulation[73,74].

Following these lines of evidence, the primary objective of this study was to test if multisession anodal tDCS of the right DLPFC during emotional working memory (WM) training could improve top-down stress regulation in healthy military personnel. The secondary objective was to explore the predictive value of the theta/beta ratio on inter-individual variability in tDCS-effects, in addition to the previously identified tDCS-response predictors age, baseline performance and education.

MATERIALS AND METHODS

PARTICIPANTS

Active-duty military personnel (18-60 years, uncorrected normal hearing) were recruited between January 2020 and April 2021[a]. Exclusion criteria were: Alcohol or drug dependence, psychoactive medication or drug use within the past two weeks, (history of) a psychiatric or neurological disorder (except for ADHD) or serious head trauma, large or ferromagnetic metal parts in the head, implanted cardiac pacemaker or neurostimulator, pregnancy, neurostimulation in the past month or skin damage or diseases at intended electrode sites. All participants provided written informed consent and received €65 for participation. The authors assert that all procedures contributing to this work complied with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The medical ethical committee of the University Medical Center Utrecht approved the study. **Table 1** shows demographics and baseline psychological characteristics for each tDCS group.

a. This study was part of a double-blind randomized controlled trial that was pre-registered at the Netherlands Trial Register (www.trialregister.nl) with ID: NL8028. The a priori computed required sample size to detect tDCS effects on stress regulation was 62. Appendix section 1.1. describes how the required sample size was computed.

Table 1. Participant characteristics (count or mean±standard deviation)

		Real tDCS	Sham tDCS
Gender	Male:	35	33
	Female:	2	2
Age (years)		34.0±10.7	36.1±11.1
Educational level[a]	High school diploma	2	3
	Vocational degree	20	21
	Associate's degree	2	0
	Bachelor's degree	6	4
	Master's degree	7	7
Number of deployments	Never deployed:	16	11
	1 deployment:	6	8
	2-3 deployments:	8	9
	≥4 deployments:	6	7
Rank[b]	Officer:	8	6
	Student-officer:	3	3
	Senior NCO:	17	20
	Junior NCO:	9	6
Handedness[c]	Right-handed:	33	30
	Left-handed:	4	4
	No preference:	0	1
ASI-3 (rating 0-4)	Physical:	0.3±0.4	0.3±0.4
	Cognitive:	0.2±0.3	0.2±0.3
	Social:	0.8±0.5	0.9±0.7
ACS (rating 1-4)	Focusing:	2.7±0.4	2.6±0.5
	Shifting:	2.8±0.3	2.8±0.4
ERQ (rating 1-7)	Reappraisal:	4.7±0.9	4.8±0.8
	Suppression:	3.6±1.0	3.7±1.0
PANAS (rating 1-5)	PA:	3.7±0.5	3.7±0.4
	NA:	1.5±0.4	1.5±0.5
Shock intensity	Current (mA):	8.2±3.5, range: 3–30	8.3±4.6, range: 2–39
	Duration (μs):	754±452, range: 200–2000	644±424, range: 200–2000
Fear of shock (rating 0-10)		2.7±1.6	3.2±1.8
Pain of shock (rating 0-10)		1.7±0.9	2.8±1.4
Start performance N-back task (block 1, session 1)	d' ($z_{hits} - z_{false\ alarms}$)	1.35±1.0	1.29±1.0

[a]: Educational levels were assessed based on the Dutch educational system and for international interpretability converted to the best corresponding American degree. [b]: NCO = non-commissioned officer. [c]: Participants were asked to identify themselves as left-handed, right-handed or no preference. ASI-3: Anxiety Sensitivity Inventory-3, ACS: Attentional control scale, ERQ: Emotion regulation questionnaire, PANAS: Positive and Negative Affect Schedule.

NON-INVASIVE BRAIN STIMULATION

TDCS was administered at an intensity of 2.0 mA (impedance <10 kΩ) for a duration of 20 minutes with a DC-stimulator Plus (NeuroConn GmbH, Ilmenau, Germany). Anodal tDCS was concentrated on an area in the right DLPFC that has been shown to be activated by both WM-performance and top-down emotion regulation[13,18,75]. The electrode montage to target this area was selected based on simulations of the electric field distribution in SimNIBS 3.2.3[76], see **Figure 1B**. A 3×3 cm saline-soaked sponge-covered anode was placed over EEG position F4, and a 5×7 cm cathode was placed dorsal of C2, see **Figure 1B**. Sham tDCS involved a 16-second fade-in fade-out stimulation at the start and end of the stimulation period, interleaved by 15 ms pulses of 0.11 mA. Changes in emotional state (STAI-6[77]) and possible tDCS side effects[78] (scored from 1, "absent", to 4, "severe") were assessed in each session.

EMOTIONAL WORKING MEMORY TRAINING

During tDCS, participants performed an emotional WM task based on the visuospatial/auditory *N*-back task from Schweizer and coworkers[18]. In each trial, participants indicated whether the location of an angry face in a 4×4 grid on a computer screen or a one-syllable negative word (e.g., "death", "fear", "hate") matched with *N* trials back, see **Figure 1B**. Based on response accuracy, *N* increased or decreased by 1 in the consecutive block. The task contained 10 blocks of 20+*N* trials per block with 6 target trials. To further increase emotional arousal during the task, unpredictable aversive screams (~80 dB, ~1 sec.) and negative fictitious performance feedback were presented during six of the blocks[79], see also Appendix section 1.2. At post-assessment, *N*-back task performance was tested on four prespecified WM-load levels (*N*=1-4).

PRIMARY OUTCOME MEASURE: THREAT-OF-SHOCK PARADIGM

Stress-related responses were assessed by the NPU-threat test[80]. The test contained two 7-minute sequences. Per sequence, three No-shock (N) blocks were alternated by two Predicable- (P) and two Unpredictable-shock (U) blocks. In a work-up procedure, electrical shocks were tuned to an intensity rated by the participant as 4 on a 5-point Likert scale (1: "I feel no shock", 5: "the shock feels very uncomfortable but not painful"). During each 60-second block, three cues were presented (4 seconds), interleaved by variable inter-trial-intervals (ITI, 3-30 seconds). One or two shocks were delivered per threat block at a computer-randomized moment during the last second of cue presentation (Predictable shock) or during the ITI (Unpredictable shock). Six shocks were delivered per threat condition in total. Appendix section 1.3.1. describes further test details.

Physiological threat responses were assessed by the eyeblink fear-potentiated startle reflex[81]. Eyeblink startles were recorded by electromyography (EMG) of two active 4 mm flat surface Ag/AgCl electrodes (BioSemi B.V., Amsterdam, the Netherlands) filled with conductive gel, placed ~1 cm apart on the left orbicularis oculi muscle[82]. A startle probe of 50 ms white noise at ~100 dB was delivered through 3A insert earphones (E-A-RTONE™, 3M™) at a computer-randomized moment during the first three seconds of each cue, and during each ITI. EMG data were preprocessed (Appendix section 1.3.3.) and startle amplitudes were quantified

as the maximum amplitude between 20 and 120 ms after probe onset (baseline-corrected and within-subject standardized)[82]. Subjective fear for each condition and context (cue, ITI) was self-reported after every sequence on a visual analogue scale (VAS) from 0: "I did not feel nervous or anxious at all" to 100: "I felt very nervous or anxious".

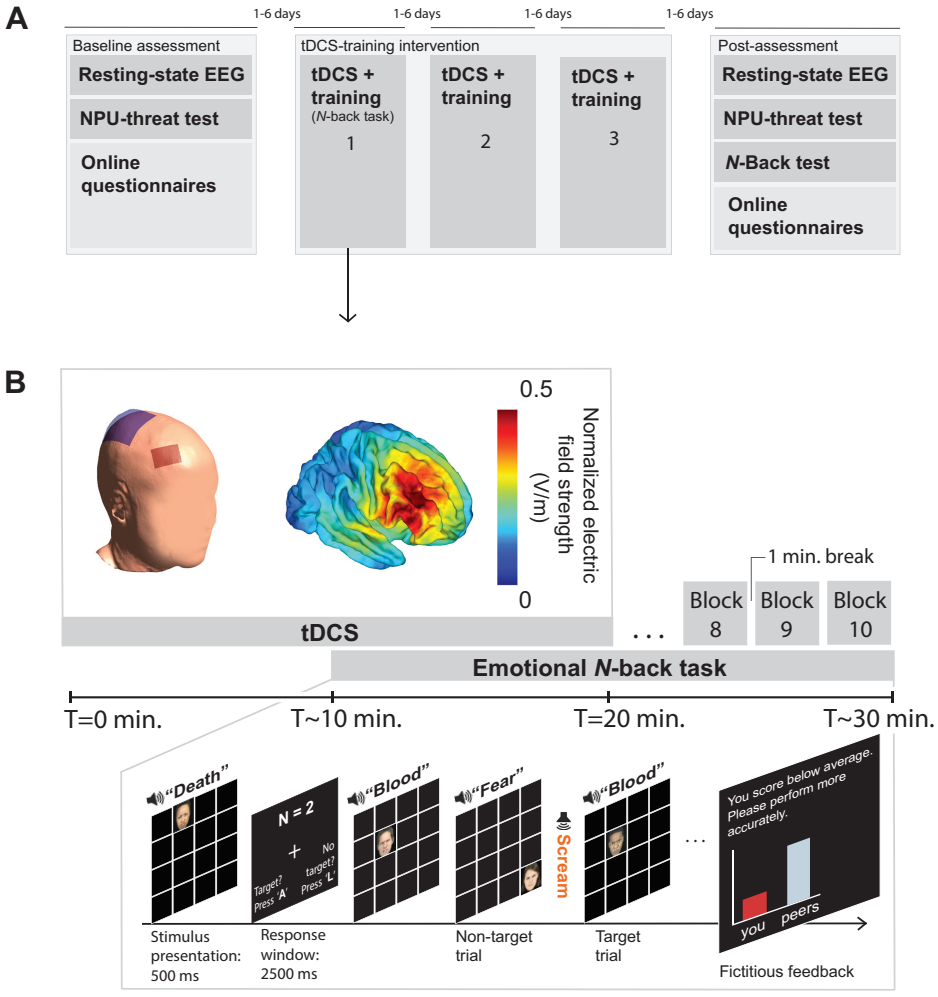

Figure 1. A) Overview of the study design. B) Overview of a tDCS-training session. The tDCS montage and example of electrical field distribution are simulated in SimNIBS 3.2.3[76] with twenty brains obtained from a publicly available MRI dataset of neurologically healthy individuals[124]. The figure displays the average electrical field distribution across these twenty simulations. The example of an *N*-Back trial sequence represent a WM-load of *N*=2. Angry face stimuli are derived from the Chicago face database[125].

Similar to previous research of top-down stress regulation[8,12], a psychoeducation was provided before the NPU-threat test. Stress regulation strategies were explained, for example by instructing to view a situation with a "detached, objective, impartial and scientific mindset" or think of more positive aspects of the situation[11], see Appendix section 1.3.2. Participants were instructed to use these strategies to downregulate threat-related emotional responses during the NPU-threat test.

QUESTIONNAIRES

Top-down stress regulation tendencies, anxiety sensitivity, emotional symptoms and cognitive control of attention were assessed by self-report on the Dutch translation of the emotion regulation questionnaire (ERQ)[83,84], the 18-item Anxiety Sensitivity Inventory (ASI-3)[85,86], the Positive and Negative Affect Schedule (PANAS)[87], and the attentional control scale (ACS) (item 12 about attention during 'lectures' was adapted to 'lessons')[88].

EXPLORATORY MEASURES

Educational level and age were recorded during the baseline visit. Baseline WM-performance was defined as a *Start Performance* score based on the sensitivity ($d' = z_{hits} - z_{false\ alarms}$) at the start of the training (block 1, session 1, where all participants performed a 1-Back task). *Start Performance* scores did not significantly differ between groups (mean±SD: real tDCS 1.35±1.0, sham tDCS 1.29±1.0, $t(70)=0.26$, $p=.799$).

The theta/beta ratio was extracted from 4-minute resting-state EEG (alternating 1-minute eyes open, 1-minute eyes closed), recorded at the start of the baseline and post-assessment visits (experimenters left the room). EEG data were recorded and amplified with a BioSemi ActiveTwo system (BioSemi B.V., Amsterdam, the Netherlands) at 2048 Hz, relative to a Common Mode Sense (CMS) active electrode in combination with a Driven Right Leg (DRL) passive electrode, from channels Fp1, Fp2, AF3, AF4, F7, F8, F3, F4, Fz, Cz, FC1, FC2, FC5, FC6, C3, C4, CP1, CP2, CP5, CP6, P7, P8, P3, P4, Pz, PO3, PO4, O1, O2 and Oz. Offline pre-processing was done with custom Matlab scripts, EEGLAB v2021.0[89] and ERPLAB v8.10[90]. Continuous data were segmented in 1-sec epochs. Eye blinks were identified and removed based on the EEGLAB ICA function. Epochs containing artifacts due to movement or facial muscle contractions were automatically marked (>30 μV difference between adjacent samples, >100 μV difference per 200 ms signal, or absolute amplitude larger than ±75 μV) and deleted after visual inspection. A fast Fourier transform (FFT) was applied per epoch using Welch's method (Hanning taper, 50% overlap, 0.25 Hz resolution). The power spectral density ($\mu V^2/Hz$) was averaged over epochs and log-transformed. Following previous research, the frontocentral theta/beta ratio was calculated as the average theta power (4-7 Hz) divided by the average beta power (13-30 Hz) from channels Fz and Cz (data collapsed across eyes open and eyes closed conditions)[66,69]. Theta/beta ratios tended to be higher in the real versus sham tDCS group (mean±SD: real tDCS 7.7±3.1, sham tDCS 6.5±2.4, $t(70)=1.82$, $p=.074$).

PROCEDURE

Participants were recruited and study visits were carried out at several military bases in the Netherlands. After providing study information, screening and obtaining informed consent, eligible individuals were randomly allocated to real or sham tDCS (1:1) by selecting the next-available stimulator-activating code from a list. This list contained 20 codes for real tDCS and 20 codes for sham tDCS, which were randomized with the Matlab function 'randsample'. Experimenters and participants were blind for code-to-condition correspondence. Baseline and post-assessment visits took place 1-6 days before and after the tDCS-training intervention and included a resting-state EEG recording and the NPU-threat test. Self-report questionnaires were completed online. Three tDCS-training sessions took place 1-6 days apart during working hours (between 6am and 9pm, depending on working shift). As it is not yet clear whether online tDCS or offline tDCS is most effective to modulate cognitive performance[91–93], tDCS (20 minutes) was turned on approximately 10 minutes before the emotional *N*-Back training was started such that tDCS continued during the first half of *N*-Back task performance and was turned off during the second half of the task, see **Figure 1B**. The emotional *N*-Back test version was carried out during the post-assessment visit. Participants were debriefed about their tDCS condition (real or sham) and the fictitious nature of the *N*-Back performance feedback after data collection was completed.

DATA REDUCTION AND STATISTICAL ANALYSIS

Data were analyzed in generalized linear mixed-effects models (GLMMs) based on a gamma distribution in R[94] using the "lme4" package[95]. Within-subject outliers in dependent variables (>3 standard deviations from the mean) were excluded. Effects are reported as significant when $p<.05$ (two-tailed). Significant interaction effects were followed-up by post-hoc comparisons of the estimated marginal means using the "emmeans" package[96] and reported with Cohen's *d* effect sizes.

Emotional working memory

The effects of tDCS were examined for both *N*-Back training performance and *N*-Back post-assessment performance. *N*-Back training performance was operationalized as the achieved WM-load level (*N*) per block, and analyzed by fixed effects for *Group* (real versus sham tDCS), *Session* (sessions 1, 2 and 3), *Block* (1-10) and the quadratic term $Block^2$ to model the typical nonlinear learning curve during training sessions. Inter-individual variability in performance levels and in learning rates were modeled by a random intercept for *Participant* and a random slope for *Block*. *N*-Back post-assessment performance was operationalized as the correct-response median reaction time (RT) and the sensitivity ($d' = z_{hits} - z_{false\ alarms}$) reflecting the ability to distinguish target trials from non-target trials[97], analyzed by fixed effects for *Group*, *WM-load* (*N*=1-4) and the maximum WM-load during training (*Train Max.*), together with a random intercept for *Participant.*

NPU-threat test

Startle amplitudes and fear ratings were significantly higher in the threat compared to safe conditions, see **Figure 3A** and Appendix section 2.4.1. To test the effects of tDCS, threat cue responses were analyzed by fixed effects for *Group*, *Threat Condition* (Predictable- or Unpredictable-shock), *Time* (baseline, post-assessment), *Sequence Number* (1 or 2), and *Probe Number* (1-6). Variability in threat responsivity and startle habituation were modeled by a random intercept for *Participant* (fear ratings) and a random slope for *Probe Number* (startle amplitudes).

Exploratory analyses

To explore the predictive value of the theta/beta ratio on tDCS-effects during the tDCS-training sessions, the theta/beta ratio was entered to the GLMM analyzing *N*-Back training performance as described above. Interactions between the theta/beta ratio and effects of tDCS-group over time (over blocks or sessions) would indicate a predictive value of the theta/beta ratio. In addition, the predictive values of *Age, Education* and *Start Performance* were evaluated following the same procedure.

RESULTS

Participants tolerated tDCS well. We noticed a small skin lesion on the anode location in one participant, likely resulting from an insufficiently soaked sponge pad during administering tDCS in session 3. The lesion healed within six days. Some participants reported mild burning, itching and tingling sensations, rated on average between 1("absent") and 2("mild"). No significant group differences appeared in these or other tDCS side effects or emotional state fluctuations during tDCS sessions, see Appendix section 2.1.

Three of the 79 included volunteers failed to comply to the *N*-Back task instructions and four dropped out prematurely, due to coronavirus-related restrictions (n=2), lack of time (n=1), or no reason provided (n=1). Ten participants showed insufficient (<30%) valid startle responses (n=2) or encountered technical issues during NPU-threat test recordings (n=8), resulting in a sample of n=62 for analysis of the primary outcome measure. For the other outcome measures, data from 72 participants was available for statistical analyses (real tDCS: n=37, sham tDCS: n=35). **Figure S1** shows the full CONSORT flow diagram.

EMOTIONAL WORKING MEMORY PERFORMANCE

TDCS-training sessions

Results showed significant interaction effects of *Group*×*Session* and *Group*×*Block*^{2} (*p*'s<.016, see **Table S2.2.1** and **Figure 2A**). In separate GLMMs per session, the *Group*×*Block*^{2} interaction showed a trend-like effect in tDCS-training sessions 1 and 3 (*p's*<.059, see **Table S2.2.2.**). **Figure 2A** shows that *N*-Back training performance tended to be higher in the real versus sham tDCS group in the first tDCS-training session (*p*=.081). This trend was not observed

in the subsequent sessions (*p*'s>.40, see **Table S2.2.3**). Results did not significantly differ when data were analyzed separately for performance during online tDCS (blocks 1-5) or offline tDCS (blocks 6-10), see Appendix section 2.2.1. Together these results show no significant group difference, but suggest that the real versus sham tDCS group tended to improve *N*-Back performance faster during the first tDCS-session.

Post-assessment

No significant main or interaction effects of *Group* were found for either RT or *d*' (*p*'s>.29), see **Figure 2B** and **Table S2.3.1**. Excluding data from participants who achieved a relatively low maximum WM-load level (*Train max.*<4, real tDCS: n=9, sham tDCS: n=3) did not significantly change the results.

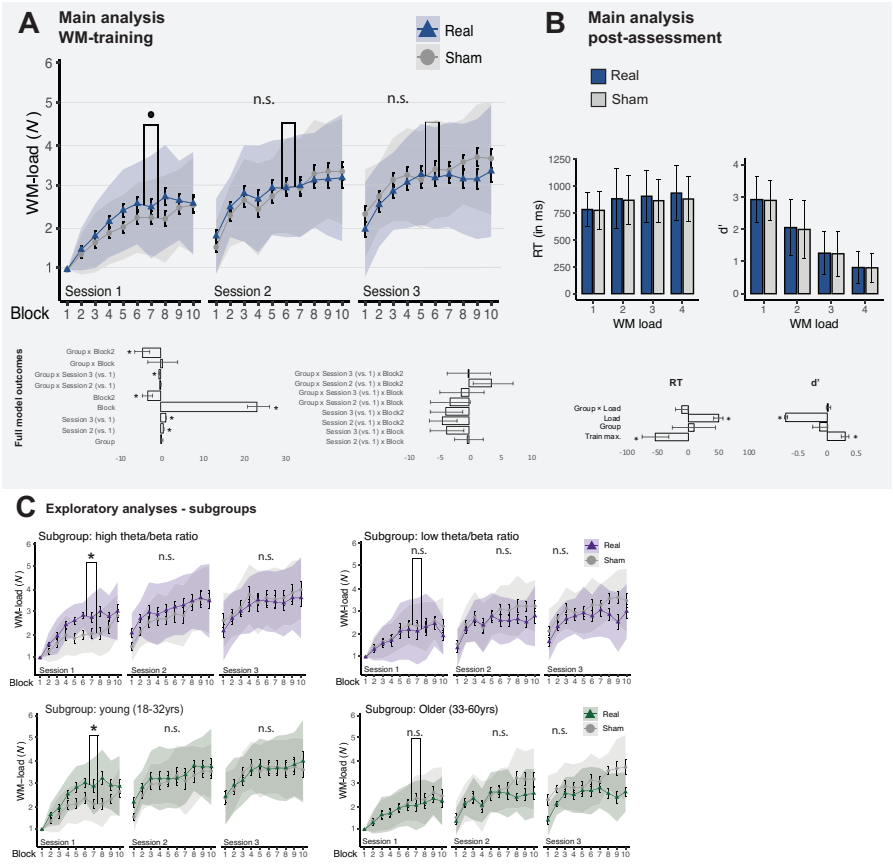

Figure 2. A) *N*-Back performance level during training per session. Error bars represent the standard error around the mean. Ribbons represent the standard deviation. B) RT and d' per WM-load in the post-assessment *N*-Back test. Error bars represent the standard deviation. C) WM-load level during emotional *N*-Back training per session, separated for median-split subsamples based on the theta/beta ratio (above) and age (below). *: *p*<.005; •: *p*<.10; n.s.=not significant. Full model outcomes represent the estimated effects (*b*) with associated standard errors. Bars with a star (*) represent statistically significant effects (*p*<.05).

NPU-THREAT TEST

Significant *Group*×*Time* interactions were found for startle amplitudes and fear ratings (*p*'s<.038, see **Figure 3B** and **Table S2.4.3**.). Follow-up comparisons revealed that the real versus sham tDCS group showed lower baseline startle amplitudes (*p*'s<.035) and lower baseline fear ratings (*p*=.050) in response to the Predictable-shock cues, see **Figure 3B** and **Table S2.4.4**. Post-assessment results showed no significant effects of real versus sham tDCS on startle amplitudes (*p*'s>.141) or fear ratings (*p*'s>.075).

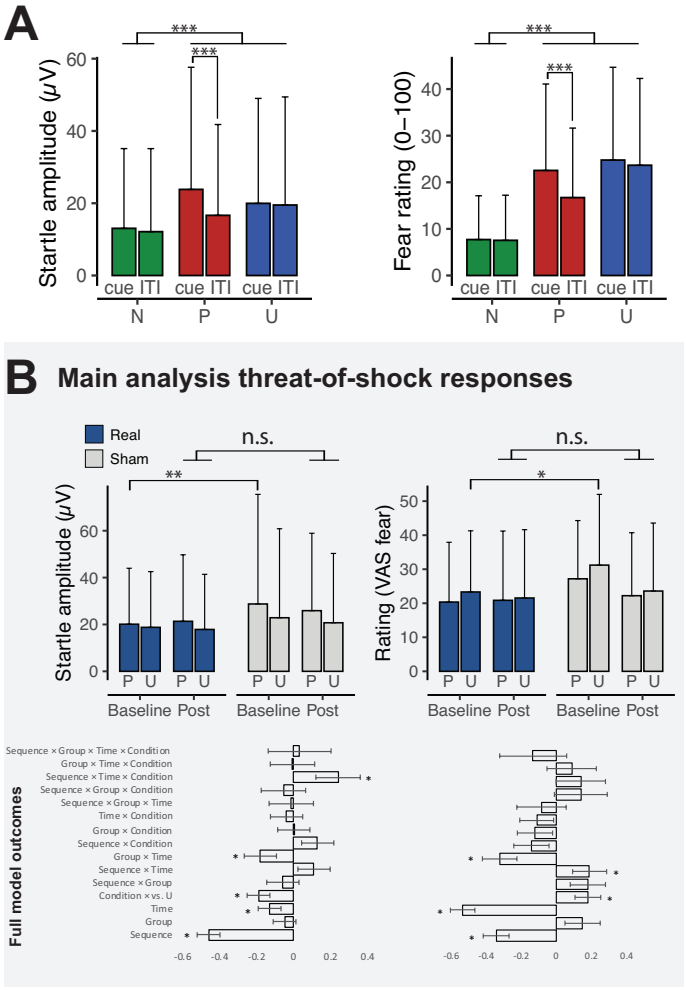

Figure 3. Startle response amplitudes and fear ratings per condition of the NPU-threat test (A) and per tDCS group (B). Error bars represent the standard deviation. ITI: Inter-trial interval. N: No-shock condition; P: Predictable-shock condition; U: Unpredictable-shock condition. ***: *p*<.001; **: *p*<.01; *: *p*<.05; n.s.= not significant. Full model outcomes represent the estimated effects (*b*) with associated standard errors. Bars with a star (*) represent statistically significant effects (*p*<.05).

EXPLORATORY ANALYSES: PREDICTORS OF TDCS EFFECT

Exploratory results indicated that the baseline theta/beta ratio influenced the effect of real tDCS on *N*-Back training performance. In the full model, significant three-way interactions were observed of *Theta/beta Ratio* with *Group* and *Session* (*Group*×*Session*×*Theta/beta ratio*: *b*(SE)=-0.11(0.04), *p*=.013) and with *Group* and *Block* (*Group*×*Block*^{2}×*Theta/beta ratio*: *b*(SE)=-0.11(0.04), *p*=.013, see **Table S2.5.1.**). To interpret these interactions, *N*-Back training performance was plotted per session, separately for median-split subsamples based on baseline theta/beta ratio, see **Figure 2C**. Follow-up group comparisons indicated that the real tDCS group only showed significantly improved performance relative to the sham tDCS group during session 1 (not during later sessions, see also **Table S2.5.3**) in participants with a higher baseline theta/beta ratio. Results showed no evidence for changes in theta/beta ratios from baseline to post-assessment; no significant effect on theta/beta ratios was observed for *Time*, *Group*, or their interaction (*Time*: *b*(SE)=0.52(0.36), *p*=.149; *Group*: *b*(SE)=0.06(0.06), *p*=.284; *Time*×*Group*: *b*(SE)=-0.13(0.08), *p*=.111).

Additionally, results of the second part of these exploratory analyses followed previous findings by showing an influence of *Age, Education* and *Start Performance* on the effect of real tDCS on *N*-Back training performance. For all three predictors, results showed significant four-way interactions with *Group*, *Session* and *Block* (*p*'s<.010, see **Table S2.5.2.**). Visual inspection of *N*-back training performance per median-split subsamples and follow-up group comparisons indicated that improved performance in the real vs. sham tDCS group during session 1 was shown by participants with lower educational level, younger age and higher start performance (see **Table S2.5.3**). This predictor-dependent group difference was most pronounced for *Age* (see **Table S2.5.3**), as illustrated in **Figure 2C**.

DISCUSSION

The present study examined changes in top-down stress regulation in healthy military personnel after three sessions of anodal tDCS over the right DLPFC at 2 mA combined with emotional WM training. Contrary to our hypothesis, results indicated no significant effect of real *versus* sham tDCS combined with WM training on stress regulation; stress-related responses to a threat-of-shock paradigm with instructed emotional downregulation did not differ between groups. Moreover, at group-level, results indicated no significant effect of real *versus* sham tDCS on emotional WM performance during the training or at post-assessment. Interestingly, however, post-hoc exploratory analyses of potential predictors of the tDCS-response including the theta/beta ratio suggested a trait-dependent effect of tDCS on performance during the *first* tDCS-WM training session. The present findings suggest that tDCS as applied here may have only a short-lasting and trait-dependent effect during the early stages of the tDCS-training intervention.

TDCS-EFFECTS ON STRESS REGULATION

No significant real versus sham tDCS effects were observed at post-assessment in the intensity or habituation of threat-related responses during the NPU-threat test. Although the NPU-threat manipulation was successful, our sample showed on average relatively low startle amplitudes (<30 μV) and fear ratings (<30 on a 0-100 scale) in response to the threat conditions compared to other healthy participant samples (average startle amplitudes of almost 50 μV, fear ratings between 4-5 on a 0-10 scale)[98,99]. While the stress regulation instructions may have lowered the intensity of threat responses in the present study[8,9], the low threat responses could also be a result of overall lower anxiety sensitivity in our sample (ASI-3 total scores mean±SD: 8.1±6.0) compared to other non-military Dutch healthy participant samples (mean±SD: 10.7±8.1)[86]. Hence, our participants may have required little improvement in top-down stress regulation to attenuate the already low threat responses. Considering that stress resilience is part of military training and selection, threat manipulations that elicit stronger stress responses may be necessary for studies in healthy military populations. Moreover, it should be noted that our results may not generalize to individuals with higher threat-sensitivity or stress regulation problems.

TDCS-EFFECTS ON EMOTIONAL WORKING MEMORY TRAINING

When taking into account predictive factors of tDCS-response, tDCS showed beneficial effects on emotional WM-performance, but this effect was limited to the first training session. This short-lived tDCS-effect contrasts results from four prior studies showing significant tDCS-induced performance gains that accumulated during WM-training and that were sustained in the days or even months after the tDCS-training intervention[44–46,100]. These studies administered anodal tDCS over the right[44,45,100] or left[44–46] DLPFC over multiple (4 to 7) sessions in healthy volunteers, similar to the present study. Unlike the present study, effects were measured in students, and different reference (cathode) locations were used (over the parietal cortex, contralateral to the anode, or surrounding the anode, i.e., high-definition tDCS). However, since two of the same research groups did not replicate their results in later studies using similar samples and electrode montages[48,49], these differences in study characteristics do not seem to explain the difference in study results.

The short-lasting tDCS-effect in the present study could also reflect that participants already reached ceiling performance during the first *N*-Back training session. It has been shown that *N*-Back ceiling performance can be achieved within 20 minutes of the task[101] and we observed a significant flattening of performance improvement towards the end of the first session. On the other hand, the emotional dual *N*-Back task was based on a working memory training study by Schweizer and coworkers[18]. Maximum performance levels in that study (*N* between 4 and 5) were higher than the performance levels reached in our sample at the end of the first tDCS-training session (*N* between 2 and 3, see **Figure 2A**). In addition, our participants further increased in *N*-Back performance from the first to the second and third session (session 3: *N* between 3 and 4, see **Figure 2A**). These results suggest that participants did not yet reach ceiling performance during the first tDCS-training session, and therefore do not support the

idea that ceiling performance explains the lack of tDCS-effects on WM-performance beyond the first tDCS-training session.

Interestingly, our results concur with a set of studies showing similar short-lasting tDCS-effects. For example, three studies in healthy students showed that multiple (2, 3 or 10) sessions of anodal tDCS over the left DLPFC (1-2 mA) significantly enhanced WM-performance during the first session, but not in subsequent sessions[102–104]. Another study showed that anodal tDCS over the left DLPFC (1.5 mA) only significantly enhanced cognitive task performance when real tDCS was applied in the first of two experimental sessions in a cross-over design[105]. The authors of this study proposed that tDCS may primarily facilitate performance at the onset of learning new cognitive skills. In line with this idea, our results show that the early-stage tDCS-effect was driven by a steeper learning curve, suggesting accelerated learning. Evidence from motor cortex stimulation research supports the idea that performing a learning task during tDCS mediates tDCS-related changes in task performance[106,107]. Moreover, effects of non-invasive brain stimulation, including tDCS-effects on WM-performance, have been shown to depend on arousal and stress levels[108–111]. In the present study, central nervous system arousal could have been elevated in particular during the first session due to the novelty of tDCS and the training task. Altogether, factors like novel learning processes and arousal could have interacted with the neurophysiological effects of tDCS specifically during the early stages of the tDCS-training intervention. More insights in these potential interactions may help to unravel how beneficial tDCS-effects can be extended beyond the short-lasting performance enhancement observed here.

INFLUENCE OF INDIVIDUAL CHARACTERISTICS ON TDCS-RESPONSE

In addition to the confirmatory group-level analyses, post-hoc analyses were performed to explore sources of individual differences in tDCS-response. These exploratory analyses indicated that the early-stage tDCS-effect on emotional WM-performance was stronger in relation to higher theta/beta ratios. Higher theta/beta ratios have repeatedly been associated with higher reward motivation[69,70,112]. Previous findings showed that reward motivation increases working memory performance and related PFC activity[113] and may promote tDCS-effects on working memory[114,115], which might explain the predictive value of the theta/beta ratio in the present study. Moreover, higher theta/beta ratios have been associated with lower cognitive control, possibly indicating that individuals with dominant subcortical-based drives relative to cortical-based cognitive control benefited more from tDCS[67,68]. Additionally, in line with previous findings, higher baseline WM-performance[54,116], younger age[52,53] and lower educational level were associated with a stronger early-stage tDCS-effect. Accordingly, several findings suggest that factors like a shorter brain-to-skull distance[117] and higher levels of neural plasticity[118,119,118] may contribute to the higher effectivity of tDCS observed in the younger adults. Instead, results on the influence of education and baseline WM-performance on tDCS-response are mixed[55,57,58]. Our finding of larger tDCS-response in individuals with higher baseline WM-performance is in line with some previous studies[54,59], and may indicate that higher recruitment of the targeted frontoparietal pathways facilitates tDCS-effects[54].

However, such explanations remain largely speculative as the present study does not identify the processes underlying the interaction between tDCS and these factors. Moreover, our results do not elucidate to what extent the four examined predictors reflect overlapping or distinct factors that influence tDCS-response.

Clearly, replication of these exploratory results is required before firm conclusions can be drawn. Nevertheless, these findings highlight the importance of involving individual state- and trait-dependent factors in understanding the effects of tDCS. Interestingly, by replicating the association between the theta/beta ratio and effects of transcranial electric stimulation on cognitive performance[73,74], our results motivate further research to establish whether this resting-state EEG-readout is a useful predictor of tDCS-response.

LIMITATIONS

The present study is disadvantaged by some methodological considerations. First, ramp-up-ramp-down stimulation was applied in the sham tDCS condition. Although this sham method is commonly used[120], results about blinding success have been mixed[121–123]. Blinding success was not formally assessed in the present study and a possible effect of unsuccessful blinding can therefore not be completely ruled out. Second, the effectivity of anodal tDCS over the DLPFC on working memory tasks performance depends on the electric field strength and consequent excitability changes in a relatively ventrally located area of the DLPFC[38,43]. Based on a priori electric field modelling estimations (**Figure 1B**), the applied electrode montage should induce peak level electrical field strength in this region. Unfortunately, the actual electrical field strength in this region in individual participants in our study is unknown, and could not be estimated due to the lack of anatomical scans. Third, a tDCS-training intervention with three sessions is comparable to previous studies (2-10 sessions, see above). However, not all studies show a significant effect of tDCS starting from the first session onwards. For example, careful examination of findings in two previous studies shows that a clear effect of tDCS on WM-performance started to manifest after three or more sessions[44,46]. Together with the potential ceiling performance issues on the NPU-threat test and *N*-Back task, this suggests that future studies may benefit from applying more tDCS-training sessions and using more sensitive outcomes measures (e.g., more variety or cognitive challenge in the tasks) to get better insight in the effect of multisession tDCS on WM-training. Finally, the present study applied tDCS both online and offline, that is, tDCS administration only covered the first half of the *N*-Back training in each session. Online and offline tDCS were combined as it is not yet clear which timing of tDCS has better effects on cognitive performance[91–93]. However, many previous tDCS-WM training studies in healthy individuals applied tDCS online only[44–46,102,103] or offline only[100]. The generalizability of our results may therefore be limited to this specific online/offline tDCS application.

CONCLUSION

The present study in healthy military personnel showed no evidence for the hypothesized beneficial effect on top-down stress regulation of multisession anodal tDCS over the right

DLPFC during emotional working memory training. Instead, the results suggest that tDCS had a short-term beneficial effect on emotional working memory performance in the early stages of the training. This effect was moderated by the theta/beta ratio and other previously identified predictors of tDCS-response, emphasizing the importance of state- and trait-dependent factors in tDCS-effects on cognitive performance.

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Conflicts of Interest: None

Appendix: The appendix presents additional details of the used materials and methods and a description of analyses results and numerical outcomes not reported in the main manuscript.

REFERENCES

1. Reijnen A, Rademaker AR, Vermetten E, Geuze E. Prevalence of mental health symptoms in Dutch military personnel returning from deployment to Afghanistan: a 2-year longitudinal analysis. *Eur Psychiatry*. 2015;30(2):341-346. doi:10.1016/j.eurpsy.2014.05.003

2. Bartone PT, Adler AB, Vaitkus MA. Dimensions of Psychological Stress in Peacekeeping Operations. *Military Medicine*. 1998;163(9):587-593. doi:10.1093/milmed/163.9.587

3. Martin K, McLeod E, Périard J, Rattray B, Keegan R, Pyne DB. The Impact of Environmental Stress on Cognitive Performance: A Systematic Review. *Human Factors: The Journal of the Human Factors and Ergonomics Society*. 2019;61(8):1205-1246. doi:10.1177/0018720819839817

4. Sareen J, Cox BJ, Afifi TO, et al. Combat and peacekeeping operations in relation to prevalence of mental disorders and perceived need for mental health care: findings from a large representative sample of military personnel. *Arch Gen Psychiatry*. 2007;64(7):843-852. doi:10.1001/archpsyc.64.7.843

5. van der Wal SJ, Vermetten E, Elbert G. Long-term development of post-traumatic stress symptoms and associated risk factors in military service members deployed to Afghanistan: Results from the PRISMO 10-year follow-up. *European Psychiatry*. 2021;64(1):e10. doi:10.1192/j.eurpsy.2020.113

6. Webb TL, Miles E, Sheeran P. Dealing with feeling: A meta-analysis of the effectiveness of strategies derived from the process model of emotion regulation. *Psychological Bulletin*. 2012;138(4):775-808. doi:10.1037/a0027600

7. Gross JJ. Emotion regulation: Affective, cognitive, and social consequences. *Psychophysiology*. 2002;39(3):S0048577201393198. doi:10.1017/S0048577201393198

8. Shurick AA, Hamilton JR, Harris LT, Roy AK, Gross JJ, Phelps EA. Durable effects of cognitive restructuring on conditioned fear. *Emotion*. 2012;12(6):1393-1397. doi:10.1037/a0029143

9. Lissek S, Orme K, Mcdowell DJ, et al. Emotion regulation and potentiated startle across affective picture and threat-of-shock paradigms. *Biological Psychology*. 2007;76(1-2):124-133. doi:10.1016/j.biopsycho.2007.07.002

10. Kalisch R, Müller MB, Tüscher O. A conceptual framework for the neurobiological study of resilience. *Behavioral and Brain Sciences*. 2015;38:e92. doi:10.1017/S0140525X1400082X

11. Denny BT, Ochsner KN. Behavioral effects of longitudinal training in cognitive reappraisal. *Emotion*. 2014;14(2):425-433. doi:10.1037/a0035276

12. Raio CM, Orederu TA, Palazzolo L, Shurick AA, Phelps EA. Cognitive emotion regulation fails the stress test. *Proceedings of the National Academy of Sciences*. 2013;110(37):15139-15144. doi:10.1073/pnas.1305706110

13. Kohn N, Eickhoff SB, Scheller M, Laird AR, Fox PT, Habel U. Neural network of cognitive emotion regulation — An ALE meta-analysis and MACM analysis. *Neuroimage*. 2014;87:345-355. doi:10.1016/j.neuroimage.2013.11.001

14. Berboth S, Morawetz C. Amygdala-prefrontal connectivity during emotion regulation: A meta-analysis of psychophysiological interactions. *Neuropsychologia*. 2021;153:107767. doi:10.1016/J.NEUROPSYCHOLOGIA.2021.107767

15. Arnsten AFT. Stress weakens prefrontal networks: molecular insults to higher cognition. *Nature Neuroscience*. 2015;18(10):1376-1385. doi:10.1038/nn.4087

16. Schmeichel BJ, Volokhov RN, Demaree HA. Working Memory Capacity and the Self-Regulation of Emotional Expression and Experience. *Journal of Personality and Social Psychology*. 2008;95(6):1526-1540. doi:10.1037/a0013345

17. Schmeichel BJ, Demaree HA. Working Memory Capacity and Spontaneous Emotion Regulation: High Capacity Predicts Self-Enhancement in Response to Negative Feedback. *Emotion*. 2010;10(5):739-744. doi:10.1037/a0019355

18. Schweizer S, Grahn J, Hampshire A, Mobbs D, Dalgleish T. Training the Emotional Brain: Improving Affective Control through Emotional Working Memory Training. *Journal of Neuroscience*. 2013;33(12):5301-5311. doi:10.1523/JNEUROSCI.2593-12.2013

19. Schweizer S, Hampshire A, Dalgleish T. Extending Brain-Training to the Affective Domain: Increasing Cognitive and Affective Executive Control through Emotional Working Memory Training. *PLoS ONE*. 2011;6(9):e24372. doi:10.1371/journal.pone.0024372

20. Pe ML, Raes F, Kuppens P. The Cognitive Building Blocks of Emotion Regulation: Ability to Update Working Memory Moderates the Efficacy of Rumination and Reappraisal on Emotion. *PLoS ONE*. 2013;8(7):69071. doi:10.1371/JOURNAL.PONE.0069071

21. Cirillo P, Gold AK, Nardi AE, et al. Transcranial magnetic stimulation in anxiety and trauma-related disorders: A systematic review and meta-analysis. *Brain and Behavior*. 2019;9(6). doi:10.1002/brb3.1284

22. Doerig N, Seinsche RJ, Moisa M, Seifritz E, Ruff CC, Kleim B. Enhancing reappraisal of negative emotional memories with transcranial direct current stimulation. *Scientific Reports 2021 11:1*. 2021;11(1):1-11. doi:10.1038/s41598-021-93647-1

23. Feeser M, Prehn K, Kazzer P, Mungee A, Bajbouj M. Transcranial Direct Current Stimulation Enhances Cognitive Control During Emotion Regulation. *Brain Stimulation*. 2014;7(1):105-112. doi:10.1016/j.brs.2013.08.006

24. He Z, Lin Y, Xia L, Liu Z, Zhang D, Elliott R. Critical role of the right VLPFC in emotional regulation of social exclusion: A tDCS study. *Social Cognitive and Affective Neuroscience*. 2018;13(4):357-366. doi:10.1093/scan/nsy026

25. Vanderhasselt MA, Sanchez A, Josephy H, Baeken C, Brunoni AR, De Raedt R. Anodal tDCS over the right dorsolateral prefrontal cortex modulates cognitive processing of emotional information as a function of trait rumination in healthy volunteers. *Biological Psychology*. 2017;123:111-118. doi:10.1016/j.biopsycho.2016.12.006

26. Herrmann MJ, Simons BSE, Horst AK, Boehme S, Straube T, Polak T. Modulation of sustained fear by transcranial direct current stimulation (tDCS) of the right inferior frontal cortex (rIFC). *Biological Psychology*. 2018;139(July):173-177. doi:10.1016/j.biopsycho.2018.10.013

27. Herrmann MJ, Beier JS, Simons B, Polak T. Transcranial Direct Current Stimulation (tDCS) of the Right Inferior Frontal Gyrus Attenuates Skin Conductance Responses to Unpredictable Threat Conditions. *Frontiers in Human Neuroscience*. 2016;10(July):1-6. doi:10.3389/fnhum.2016.00352

28. Chan MMY, Yau SSY, Han YMY. The neurobiology of prefrontal transcranial direct current stimulation (tDCS) in promoting brain plasticity: A systematic review and meta-analyses of human and rodent studies. *Neuroscience & Biobehavioral Reviews*. 2021;125:392-416. doi:10.1016/J.NEUBIOREV.2021.02.035

29. Knotkova H, Nitsche MA, Bikson M, Woods AJ, eds. Practical Guide to Transcranial Direct Current Stimulation. *Practical Guide to Transcranial Direct Current Stimulation*. Published online 2019. doi:10.1007/978-3-319-95948-1

30. Nitsche MA, Cohen LG, Wassermann EM, et al. Transcranial direct current stimulation: State of the art 2008. *Brain Stimulation*. 2008;1(3):206-223. doi:10.1016/J.BRS.2008.06.004

31. Marques LM, Morello LYN, Boggio PS. Ventrolateral but not Dorsolateral Prefrontal Cortex tDCS effectively impact emotion reappraisal – effects on Emotional Experience and Interbeat Interval. *Scientific Reports*. 2018;8(1):15295. doi:10.1038/s41598-018-33711-5

32. Clarke PJF, Van Bockstaele B, Marinovic W, Howell JA, Boyes ME, Notebaert L. The effects of left DLPFC tDCS on emotion regulation, biased attention, and emotional reactivity to negative content. *Cognitive, Affective and Behavioral Neuroscience*. 2020;20(6):1323-1335. doi:10.3758/s13415-020-00840-2

33. Clarke PJF, Haridas SMP, Van Bockstaele B, Chen NTM, Salemink E, Notebaert L. Frontal tDCS and Emotional Reactivity to Negative Content: Examining the Roles of Biased Interpretation and Emotion Regulation. *Cognitive Therapy and Research*. 2021;45(1):19-30. doi:10.1007/s10608-020-10162-9

34. Segrave RA, Arnold S, Hoy K, Fitzgerald PB. Concurrent Cognitive Control Training Augments the Antidepressant Efficacy of tDCS: A Pilot Study. *Brain Stimulation*. 2014;7(2):325-331. doi:10.1016/j.brs.2013.12.008

35. Berryhill ME, Martin D. Cognitive Effects of Transcranial Direct Current Stimulation in Healthy and Clinical Populations: An Overview. *Journal of ECT*. 2018;34(3):e25-e35. doi:10.1097/YCT.0000000000000534

36. Bikson M, Rahman A. Origins of specificity during tDCS: anatomical, activity-selective, and input-bias mechanisms. *Frontiers in Human Neuroscience*. 2013;0(OCT):688. doi:10.3389/FNHUM.2013.00688

37. Dedoncker J, Baeken C, de Raedt R, Vanderhasselt MA. Combined transcranial direct current stimulation and psychological interventions: State of the art and promising perspectives for clinical psychology. *Biological Psychology*. 2021;158:107991. doi:10.1016/J.BIOPSYCHO.2020.107991

38. Pisoni A, Mattavelli G, Papagno C, Rosanova M, Casali AG, Romero Lauro LJ. Cognitive Enhancement Induced by Anodal tDCS Drives Circuit-Specific Cortical Plasticity. *Cerebral Cortex*. 2018;28(4):1132-1140. doi:10.1093/cercor/bhx021

39. Li LM, Violante IR, Leech R, et al. Brain state and polarity dependent modulation of brain networks by transcranial direct current stimulation. *Human Brain Mapping*. 2019;40(3):904-915. doi:10.1002/hbm.24420

40. Monte-Silva K, Kuo MF, Hessenthaler S, et al. Induction of Late LTP-Like Plasticity in the Human Motor Cortex by Repeated Non-Invasive Brain Stimulation. *Brain Stimulation*. 2013;6(3):424-432. doi:10.1016/j.brs.2012.04.011

41. van 't Wout-Frank M, Shea MT, Larson VC, Greenberg BD, Philip NS. Combined transcranial direct current stimulation with virtual reality exposure for posttraumatic stress disorder: Feasibility and pilot results. *Brain Stimulation*. 2019;12(1):41-43. doi:10.1016/j.brs.2018.09.011

42. Lee TW, Xue SW. Does emotion regulation engage the same neural circuit as working memory? A meta-analytical comparison between cognitive reappraisal of negative emotion and 2-back working memory task. Papousek I, ed. *PLOS ONE*. 2018;13(9):e0203753. doi:10.1371/journal.pone.0203753

43. Wischnewski M, Mantell KE, Opitz A. Identifying regions in prefrontal cortex related to working memory improvement: A novel meta-analytic method using electric field modeling. *Neuroscience & Biobehavioral Reviews*. 2021;130:147-161. doi:10.1016/J.NEUBIOREV.2021.08.017

44. Au J, Katz B, Buschkuehl M, et al. Enhancing Working Memory Training with Transcranial Direct Current Stimulation. *Journal of Cognitive Neuroscience*. 2016;28(9):1419-1432. doi:10.1162/jocn_a_00979

45. Ruf SP, Fallgatter AJ, Plewnia C. Augmentation of working memory training by transcranial direct current stimulation (tDCS). *Scientific Reports*. 2017;7(1):876. doi:10.1038/s41598-017-01055-1

46. Ke Y, Wang N, Du J, et al. The Effects of Transcranial Direct Current Stimulation (tDCS) on Working Memory Training in Healthy Young Adults. *Frontiers in Human Neuroscience*. 2019;13:19. doi:10.3389/fnhum.2019.00019

47. Trumbo MC, Matzen LE, Coffman BA, et al. Enhanced working memory performance via transcranial direct current stimulation: The possibility of near and far transfer. *Neuropsychologia*. 2016;93:85-96. doi:10.1016/J.NEUROPSYCHOLOGIA.2016.10.011

48. Au J, Katz B, Moon A, et al. Post-training stimulation of the right dorsolateral prefrontal cortex impairs working memory training performance. *Journal of Neuroscience Research*. 2021;99(10):2351-2363. doi:10.1002/JNR.24784

49. Shires J, Carrasco C, Berryhill ME. No tDCS augmented working memory training benefit in undergraduates rewarded with course credit. *Brain Stimulation*. 2020;13(6):1524-1526. doi:10.1016/J.BRS.2020.08.015

50. Luque-Casado A, Rodríguez-Freiría R, Fogelson N, Iglesias-Soler E, Fernández-del-Olmo M. An Integrative Clustering Approach to tDCS Individual Response Variability in Cognitive Performance: Beyond a Null Effect on Working Memory. *Neuroscience*. 2020;443:120-130. doi:10.1016/J.NEUROSCIENCE.2020.07.036

51. Perceval G, Flöel A, Meinzer M. Can transcranial direct current stimulation counteract age-associated functional impairment? *Neuroscience & Biobehavioral Reviews*. 2016;65:157-172. doi:10.1016/J.NEUBIOREV.2016.03.028

52. Leach RC, McCurdy MP, Trumbo MC, Matzen LE, Leshikar ED. Differential Age Effects of Transcranial Direct Current Stimulation on Associative Memory. *The Journals of Gerontology: Series B*. 2019;74(7):1163-1173. doi:10.1093/GERONB/GBY003

53. Antonenko D, Nierhaus T, Meinzer M, et al. Age-dependent effects of brain stimulation on network centrality. *Neuroimage*. 2018;176:71-82. doi:10.1016/J.NEUROIMAGE.2018.04.038

54. Schmicker M, Menze I, Schneider C, Taubert M, Zaehle T, Mueller NG. Making the rich richer: Frontoparietal tDCS enhances transfer effects of a single-session distractor inhibition training on working memory in high capacity individuals but reduces them in low capacity individuals. *Neuroimage*. 2021;242:118438. doi:10.1016/J.NEUROIMAGE.2021.118438

55. Emonson MRL, Fitzgerald PB, Rogasch NC, Hoy KE. Neurobiological effects of transcranial direct current stimulation in younger adults, older adults and mild cognitive impairment. *Neuropsychologia*. 2019;125:51-61. doi:10.1016/j.neuropsychologia.2019.01.003

56. Brunoni AR, Tortella G, Benseñor IM, Lotufo PA, Carvalho AF, Fregni F. Cognitive effects of transcranial direct current stimulation in depression: Results from the SELECT-TDCS trial and insights for further clinical trials. *Journal of Affective Disorders*. 2016;202:46-52. doi:10.1016/J.JAD.2016.03.066

57. Splittgerber M, Salvador R, Brauer H, et al. Individual Baseline Performance and Electrode Montage Impact on the Effects of Anodal tDCS Over the Left Dorsolateral Prefrontal Cortex. *Frontiers in Human Neuroscience*. 2020;14. doi:10.3389/fnhum.2020.00349

58. Tseng P, Hsu TY, Chang CF, et al. Unleashing Potential: Transcranial Direct Current Stimulation over the Right Posterior Parietal Cortex Improves Change Detection in Low-Performing Individuals. *Journal of Neuroscience*. 2012;32(31):10554-10561. doi:10.1523/JNEUROSCI.0362-12.2012

59. Berryhill ME, Jones KT. tDCS selectively improves working memory in older adults with more education. *Neuroscience Letters*. 2012;521(2):148-151. doi:10.1016/j.neulet.2012.05.074

60. Al-Kaysi AM, Al-Ani A, Loo CK, et al. Predicting tDCS treatment outcomes of patients with major depressive disorder using automated EEG classification. *Journal of Affective Disorders*. 2017;208:597-603. doi:10.1016/j.jad.2016.10.021

61. Hordacre B, Moezzi B, Goldsworthy MR, Rogasch NC, Graetz LJ, Ridding MC. Resting state functional connectivity measures correlate with the response to anodal transcranial direct current stimulation. *European Journal of Neuroscience*. 2017;45(6):837-845. doi:10.1111/EJN.13508

62. Thut G, Bergmann TO, Fröhlich F, et al. Guiding transcranial brain stimulation by EEG/MEG to interact with ongoing brain activity and associated functions: A position paper. *Clinical Neurophysiology*. 2017;128(5):843-857. doi:10.1016/j.clinph.2017.01.003

63. Schutter DJLG, Knyazev GG. Cross-frequency coupling of brain oscillations in studying motivation and emotion. *Motivation and Emotion*. 2012;36(1):46-54. doi:10.1007/s11031-011-9237-6

64. Knyazev GG. Motivation, emotion, and their inhibitory control mirrored in brain oscillations. *Neuroscience & Biobehavioral Reviews*. 2007;31(3):377-395. doi:10.1016/j.neubiorev.2006.10.004

65. Tortella-Feliu M, Morillas-Romero A, Balle M, Llabrés J, Bornas X, Putman P. Spontaneous EEG activity and spontaneous emotion regulation. *International Journal of Psychophysiology*. 2014;94(3):365-372. doi:10.1016/j.ijpsycho.2014.09.003

66. Putman P, van Peer J, Maimari I, van der Werff S. EEG theta/beta ratio in relation to fear-modulated response-inhibition, attentional control, and affective traits. *Biological Psychology*. 2010;83(2):73-78. doi:10.1016/j.biopsycho.2009.10.008

67. Angelidis A, van der Does W, Schakel L, Putman P. Frontal EEG theta/beta ratio as an electrophysiological marker for attentional control and its test-retest reliability. *Biological Psychology*. 2016;121:49-52. doi:10.1016/j.biopsycho.2016.09.008

68. Angelidis A, Hagenaars M, van Son D, van der Does W, Putman P. Do not look away! Spontaneous frontal EEG theta/beta ratio as a marker for cognitive control over attention to mild and high threat. *Biological Psychology*. 2018;135:8-17. doi:10.1016/j.biopsycho.2018.03.002

69. Massar SAA, Kenemans JL, Schutter DJLG. Resting-state EEG theta activity and risk learning: sensitivity to reward or punishment? *International Journal of Psychophysiology*. 2014;91(3):172-177. doi:10.1016/J.IJPSYCHO.2013.10.013

70. Schutte I, Kenemans JL, Schutter DJLG. Resting-state theta/beta EEG ratio is associated with reward- and punishment-related reversal learning. *Cognitive, Affective, & Behavioral Neuroscience*. 2017;17(4):754-763. doi:10.3758/s13415-017-0510-3

71. Wischnewski M, Zerr P, Schutter DJLG. Effects of Theta Transcranial Alternating Current Stimulation Over the Frontal Cortex on Reversal Learning. *Brain Stimulation*. 2016;9(5):705-711. doi:10.1016/j.brs.2016.04.011

72. Sari BA, Koster EHW, Pourtois G, Derakshan N. Training working memory to improve attentional control in anxiety: A proof-of-principle study using behavioral and electrophysiological measures. *Biol Psychol*. 2016;121(Pt B):203-212. doi:10.1016/j.biopsycho.2015.09.008

73. Harty S, Cohen Kadosh R. Suboptimal Engagement of High-Level Cortical Regions Predicts Random-Noise-Related Gains in Sustained Attention. *Psychological Science*. 2019;30(9):1318-1332. doi:10.1177/0956797619856658

74. Sheffield JG, Raz G, Sella F, Kadosh RC. How can noise alter neurophysiology in order to improve human behaviour? A combined tRNS and EEG study. *bioRxiv*. Published online July 31, 2020:2020.01.09.900118. doi:10.1101/2020.01.09.900118

75. Buhle JT, Silvers JA, Wager TD, et al. Cognitive Reappraisal of Emotion: A Meta-Analysis of Human Neuroimaging Studies. *Cerebral Cortex*. 2014;24(11):2981-2990. doi:10.1093/cercor/bht154

76. Thielscher A, Antunes A, Saturnino GB. Field modeling for transcranial magnetic stimulation: A useful tool to understand the physiological effects of TMS? In: *2015 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*. IEEE; 2015:222-225. doi:10.1109/EMBC.2015.7318340

77. Marteau TM, Bekker H. The development of a six-item short-form of the state scale of the Spielberger State—Trait Anxiety Inventory (STAI). *British Journal of Clinical Psychology*. 1992;31(3):301-306. doi:10.1111/J.2044-8260.1992.TB00997.X

78. Brunoni AR, Amadera J, Berbel B, Volz MS, Rizzerio BG, Fregni F. A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. *The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum (CINP)*. 2011;14(8):1133-1145. doi:10.1017/S1461145710001690

79. Dickerson SS, Kemeny ME. Acute Stressors and Cortisol Responses: A Theoretical Integration and Synthesis of Laboratory Research. *Psychological Bulletin*. 2004;130(3):355-391. doi:10.1037/0033-2909.130.3.355

80. Schmitz A, Grillon C. Assessing fear and anxiety in humans using the threat of predictable and unpredictable aversive events (the NPU-threat test). *Nature Protocols*. 2012;7(3):527-532. doi:10.1038/nprot.2012.001

81. Davis M. Neural systems involved in fear and anxiety measured with fear-potentiated startle. *American Psychologist*. 2006;61(8):741-756. doi:10.1037/0003-066X.61.8.741

82. Blumenthal TD, Cuthbert BN, Filion DL, Hackley S, Lipp O V., Van Boxtel A. Committee report: Guidelines for human startle eyeblink electromyographic studies. *Psychophysiology*. 2005;42(1):1-15. doi:10.1111/j.1469-8986.2005.00271.x

83. Gross JJ, John OP. Individual Differences in Two Emotion Regulation Processes: Implications for Affect, Relationships, and Well-Being. *Journal of Personality and Social Psychology*. 2003;85(2):348-362. doi:10.1037/0022-3514.85.2.348

84. Koole SL, Jostmann NB. Getting a grip on your feelings: Effects of action orientation and external demands on intuitive affect regulation. *Journal of Personality and Social Psychology*. 2004;87(6):974-990. doi:10.1037/0022-3514.87.6.974

85. Reiss S, Peterson RA, Gursky DM, McNally RJ. Anxiety sensitivity, anxiety frequency and the prediction of fearfulness. *Behaviour Research and Therapy*. 1986;24(1):1-8. doi:10.1016/0005-7967(86)90143-9

86. Taylor S, Zvolensky MJ, Cox BJ, et al. Robust dimensions of anxiety sensitivity: Development and initial validation of the Anxiety Sensitivity Index-3. *Psychological Assessment*. 2007;19(2):176-188. doi:10.1037/1040-3590.19.2.176

87. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. *J Pers Soc Psychol*. 1988;54(6):1063-1070. doi:10.1037/0022-3514.54.6.1063

88. Derryberry D, Reed M a. Anxiety-related attentional biases and their regulation by attentional control. *J Abnorm Psychol*. 2002;111(2):225-236. doi:10.1037/0021-843X.111.2.225

89. Delorme A, Makeig S. *EEGLAB: An Open Source Toolbox for Analysis of Single-Trial EEG Dynamics Including Independent Component Analysis*. Vol 134.; 2004.

90. Lopez-Calderon J, Luck SJ. ERPLAB: an open-source toolbox for the analysis of event-related potentials. *Frontiers in Human Neuroscience*. 2014;8(1 APR):213. doi:10.3389/fnhum.2014.00213

91. Friehs MA, Frings C. Offline beats online: Transcranial direct current stimulation timing influences on working memory. *NeuroReport*. 2019;30(12):795-799. doi:10.1097/WNR.0000000000001272

92. Friehs MA, Frings C, Hartwigsen G. Effects of single-session transcranial direct current stimulation on reactive response inhibition. *Neuroscience and Biobehavioral Reviews*. 2021;128:749-765. doi:10.1016/J.NEUBIOREV.2021.07.013

93. Hill AT, Fitzgerald PB, Hoy KE. Effects of Anodal Transcranial Direct Current Stimulation on Working Memory: A Systematic Review and Meta-Analysis of Findings From Healthy and Neuropsychiatric Populations. *Brain Stimulation*. 2016;9(2):197-208. doi:10.1016/j.brs.2015.10.006

94. R Foundation for Statistical Computing. R: A language and environment for statistical computing. *R: A Language and Environment for Statistical Computing 331*. Published online 2016.

95. Bates D, Mächler M, Bolker B, Walker S. Fitting Linear Mixed-Effects Models Using lme4. *Journal of Statistical Software*. 2015;67(1). doi:10.18637/jss.v067.i01

96. Lenth R V. emmeans: Estimated Marginal Means, aka Least-Squares Means. R package version 1.7.0. Published online 2021.

97. Stanislaw H. *Calculation of Signal Detection Theory Measures*. Vol 3.; 1999.

98. Balderston NL, Liu J, Roberson-Nay R, Ernst M, Grillon C. The relationship between dlPFC activity during unpredictable threat and CO2-induced panic symptoms. *Translational Psychiatry*. 2017;7(12):1266. doi:10.1038/s41398-017-0006-5

99. Ferry RA, Nelson BD. Differential impact of threat type on defensive motivation and attention during the NPU-threat task. *Motivation and Emotion*. 2020;44(5):670-685. doi:10.1007/S11031-020-09835-5/FIGURES/6

100. Jones KT, Peterson DJ, Blacker KJ, Berryhill ME. Frontoparietal neurostimulation modulates working memory training benefits and oscillatory synchronization. *Brain Research*. 2017;1667:28-40. doi:10.1016/j.brainres.2017.05.005

101. Yamashita M, Kawato M, Imamizu H. Predicting learning plateau of working memory from whole-brain intrinsic network connectivity patterns. *Scientific Reports 2015 5:1*. 2015;5(1):1-8. doi:10.1038/srep07622

102. Talsma LJ, Kroese HA, Slagter HA. Boosting Cognition: Effects of Multiple-Session Transcranial Direct Current Stimulation on Working Memory. *Journal of Cognitive Neuroscience*. 2017;29(4):755-768. doi:10.1162/jocn_a_01077

103. Martin DM, Liu R, Alonzo A, et al. Can transcranial direct current stimulation enhance outcomes from cognitive training? A randomized controlled trial in healthy participants. *The International Journal of Neuropsychopharmacology*. 2013;16(09):1927-1936. doi:10.1017/S1461145713000539

104. Lally N, Nord CL, Walsh V, Roiser JP. Does excitatory fronto-extracerebral tDCS lead to improved working memory performance? *F1000Res*. 2013;2:219. doi:10.12688/f1000research.2-219.v2

105. Fehring DJ, Illipparampil R, Acevedo N, Jaberzadeh S, Fitzgerald PB, Mansouri FA. Interaction of task-related learning and transcranial direct current stimulation of the prefrontal cortex in modulating executive functions. *Neuropsychologia*. 2019;131(April):148-159. doi:10.1016/j.neuropsychologia.2019.05.011

106. Bortoletto M, Pellicciari MC, Rodella C, Miniussi C. The Interaction With Task-induced Activity is More Important Than Polarization: A tDCS Study. *Brain Stimulation*. 2015;8(2):269-276. doi:10.1016/J.BRS.2014.11.006

107. Buch ER, Santarnecchi E, Antal A, et al. Effects of tDCS on motor learning and memory formation: A consensus and critical position paper. *Clinical Neurophysiology*. 2017;128(4):589-603. doi:10.1016/J.CLINPH.2017.01.004

108. Schutter DJLG, Hofman D, van Honk J. Fearful faces selectively increase corticospinal motor tract excitability: A transcranial magnetic stimulation study. *Psychophysiology*. 2008;45(3):345-348. doi:10.1111/j.1469-8986.2007.00635.x

109. Coombes SA, Tandonnet C, Fujiyama H, Janelle CM, Cauraugh JH, Summers JJ. Emotion and motor preparation: A transcranial magnetic stimulation study of corticospinal motor tract excitability. *Cognitive, Affective, & Behavioral Neuroscience 2009 9:4*. 2009;9(4):380-388. doi:10.3758/CABN.9.4.380

110. Ankri YLE, Braw Y, Luboshits G, Meiron O. The effects of stress and transcranial direct current stimulation (tDCS) on working memory: A randomized controlled trial. *Cognitive, Affective and Behavioral Neuroscience*. 2020;20(1):103-114. doi:10.3758/S13415-019-00755-7/FIGURES/5

111. Esposito M, Ferrari C, Fracassi C, Miniussi C, Brignani D. Responsiveness to left-prefrontal tDCS varies according to arousal levels. *European Journal of Neuroscience*. 2022;55(3):762-777. doi:10.1111/EJN.15584

112. Schutter DJLG, Van Honk J. Electrophysiological ratio markers for the balance between reward and punishment. *Cognitive Brain Research*. 2005;24(3):685-690. doi:10.1016/J.COGBRAINRES.2005.04.002

113. Krawczyk DC, D'Esposito M. Modulation of working memory function by motivation through loss-aversion. *Human Brain Mapping*. 2013;34(4):762-774. doi:10.1002/HBM.21472

114. Di Rosa E, Brigadoi S, Cutini S, et al. Reward motivation and neurostimulation interact to improve working memory performance in healthy older adults: A simultaneous tDCS-fNIRS study. *Neuroimage*. 2019;202:116062. doi:10.1016/J.NEUROIMAGE.2019.116062

115. Jones KT, Gözenman F, Berryhill ME. The strategy and motivational influences on the beneficial effect of neurostimulation: A tDCS and fNIRS study. *Neuroimage*. 2015;105:238-247. doi:10.1016/J.NEUROIMAGE.2014.11.012

116. Jones KT, Berryhill ME. Parietal contributions to visual working memory depend on task difficulty. *Frontiers in Psychiatry*. 2012;3(SEP):81. doi:10.3389/FPSYT.2012.00081/BIBTEX

117. Opitz A, Paulus W, Will S, Antunes A, Thielscher A. Determinants of the electric field during transcranial direct current stimulation. *Neuroimage*. 2015;109:140-150. doi:10.1016/J.NEUROIMAGE.2015.01.033

118. Burke SN, Barnes CA. Neural plasticity in the ageing brain. *Nature Reviews Neuroscience 2006 7:1*. 2006;7(1):30-40. doi:10.1038/nrn1809

119. Cirillo G, di Pino G, Capone F, et al. Neurobiological after-effects of non-invasive brain stimulation. *Brain Stimulation*. 2017;10(1):1-18. doi:10.1016/j.brs.2016.11.009

120. Fonteneau C, Mondino M, Arns M, et al. Sham tDCS: A hidden source of variability? Reflections for further blinded, controlled trials. *Brain Stimulation*. Published online 2019. doi:10.1016/j.brs.2018.12.977

121. Turi Z, Csifcsák G, Boayue NM, et al. Blinding is compromised for transcranial direct current stimulation at 1 mA for 20 min in young healthy adults. *European Journal of Neuroscience*. 2019;50(8):3261-3268. doi:10.1111/EJN.14403

122. Greinacher R, Buhôt L, Möller L, Learmonth G. The time course of ineffective sham-blinding during low-intensity (1 mA) transcranial direct current stimulation. *European Journal of Neuroscience*. 2019;50(8):3380-3388. doi:10.1111/ejn.14497

123. Ambrus GG, Al-Moyed H, Chaieb L, Sarp L, Antal A, Paulus W. The fade-in – Short stimulation – Fade out approach to sham tDCS – Reliable at 1 mA for naïve and experienced subjects, but not investigators. *Brain Stimulation*. 2012;5(4):499-504. doi:10.1016/j.brs.2011.12.001

124. Hanke M, Baumgartner FJ, Ibe P, et al. A high-resolution 7-Tesla fMRI dataset from complex natural stimulation with an audio movie. *Scientific Data 2014 1:1*. 2014;1(1):1-18. doi:10.1038/sdata.2014.3

125. Ma DS, Correll J, Wittenbrink B. The Chicago face database: A free stimulus set of faces and norming data. *Behavior Research Methods*. 2015;47(4):1122-1135. doi:10.3758/S13428-014-0532-5/FIGURES/2

APPENDIX

SUPPLEMENTARY METHODS

Participants: Additional details on screening and sample size calculation

The absence of a current depressive episode, an anxiety disorder, PTSD or intermittent explosive disorder diagnoses were confirmed by structured interview questions from the M.I.N.I. based on DSM-IV[1].

Previous studies of prefrontal tDCS-effects on emotion regulation[2-6] provided an a priori estimated effect size of d=0.73. A sample size of 62 was required to detect this effect, as computed in G*Power 3.1[7] based on 80% power and a 0.05 false positive rate.

Emotional working memory task

Additional details on the task design

Following Schweizer et al.[8], the *N*-Back task started with *N*=1 (1-Back, minimum WM-load level). *N* increased or decreased by 1 in the next block after correctly responding to ≥70% or ≤50% targets and non-targets. In the second and third session, *N* started at the final *N* achieved in the previous session minus 1. Response buttons corresponding to targets and non-targets ('L' and 'A' keyboard buttons) were counterbalanced between subjects.

Additional details about the fictitious performance feedback

After each block in the *N*-Back task, participants were presented fictitious personal performance score displayed next to a fictitious peer group norm score in a bar graph. Negative performance feedback was provided in six of the blocks: the participant's fictitious score was displayed as much lower than the peer group's score in a red-colored bar, accompanied by the message: "Your accuracy or response speed is below average. Please perform the task as accurately as possible." Neutral performance feedback was provided in the remaining blocks: the participant's fictitious score was displayed as similar to the fictitious peer group's score in a grey-colored bar.

NPU-threat test

Additional details on the task design

Following Schmitz and Grillon[9], the conditions were presented in two sequences in the orders P-N-U-N-U-N-P and U-N-P-N-P-N-U or vice versa. A 1-minute break separated the two sequences. After the test, participants rated the intensity, painfulness and fear of the shock on a Likert scale from 1: "not intense/painful/ nervous or anxious at all" to 10: "very intense/ painful/ nervous or anxious".

Psychoeducation on emotion regulation strategies

Three previous studies showed that tDCS particularly modulated stress-related emotional responses when cognitive emotion regulation strategies were actively applied[2-4]. Psychoeducation in cognitive regulation strategies can improve regulation of threat responses[10] and reduce amygdala reactivity to threat[11]. Therefore, psychoeducation was given briefly during the baseline visit to familiarize all participants with cognitive regulation strategies.

Psychoeducation was based on the cognitive regulation training described in two previous studies[10,12], and adapted to the current study context in cooperation with two clinical psychologists. First, the experimenter explained that the intensity of emotional reactions to negative events can be reduced by intentionally re-evaluating the value or meaning of something in a less threatening or less negative way. The experimenter provided the 'distancing' and 'reinterpreting' strategies for emotion regulation, adopted from Denny and Ochsner. For the distancing strategy, the participant was instructed to view a stimulus or situation with a "detached, objective, impartial and scientific mindset"[13]. For the reinterpretation strategy, the participant was instructed to think of more positive aspects of the stimulus or situation, such as by "focusing on a detail or aspect of the situation or stimulus that isn't quite as bad as it first seemed"[13]. The experimenter provided an example of a negative every-day-life event, and asked the participant to use both strategies to think of the event in a less emotionally arousing way. Psychoeducation took approximately twenty minutes to complete. A short recap was given during the post-assessment visit.

Startle eye-blink data processing

Surface electrodes were measured online at 2048 Hz, relative to a Common Mode Sense (CMS) active electrode in combination with a Driven Right Leg (DRL) passive electrode. Before task onset, six startle probes were presented to stabilize startle responses[14]. EMG responses were pre-processed in a custom MATLAB script based on startle eyeblink analysis guidelines[14,15] using EEGLAB and ERPLAB functions[16,17]. First, the raw bipolar signal between the two surface electrodes was downsampled to 500 Hz, filtered with a 28 Hz high pass 4th order infinite impulse response (IIR) Butterworth filter, rectified by taking the root mean square, and smoothed by a 30 Hz low pass filter. Next, epochs were created from -1800 to 150 ms around startle probes, and the signal was corrected to the last 50 ms before probe onset. To exclude artifacts caused by, e.g., voluntary blinks, the baseline was divided into 150-ms windows; windows with signal deflections >10 μV were excluded from the baseline mean following Heesink et al.[18]. Deflections >10 μV occurring in the last 50 ms before probe onset led to exclusion of the whole epoch. On average, 3±7 epochs were excluded per participant (range excluded epochs in the real tDCS group: 0-26 epochs, in the sham tDCS group: 0-42 epochs). Finally, a baseline mean voltage was calculated as the signal mean during the 1800 ms before probe onset and subtracted from the startle amplitude value.

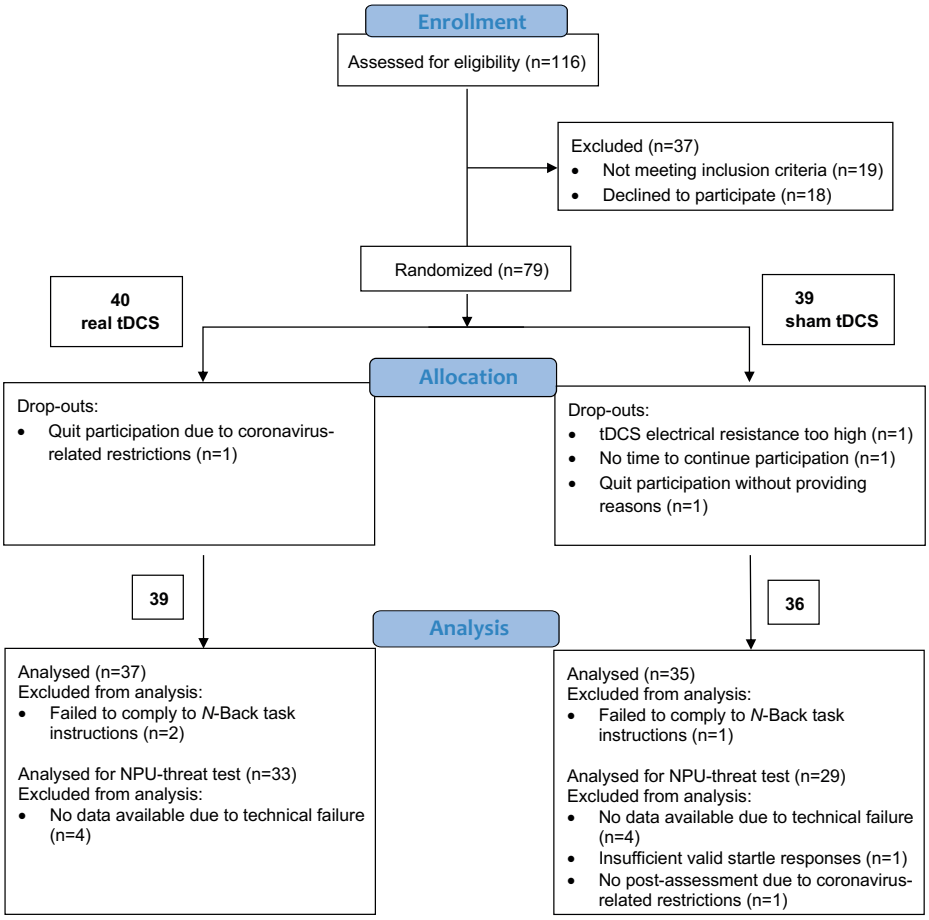


Figure S1. CONSORT flow diagram.

SUPPLEMENTARY RESULTS

EMOTIONAL STATE FLUCTUATIONS AND TDCS SIDE EFFECTS

Table S2.1.1. shows pre- to post-session fluctuations in emotional state as assessed by the STAI-6, and tDCS side effect scores. Group differences were tested by MANOVA's with all items as dependent variables (formulas: STAI-6 items ~ *Group*(real,sham) * *Session*(1,2,3) * *Time*(pre,post); tDCS side effects ~ *Group* * *Session*). The real versus sham tDCS group showed no significant differences in emotional state fluctuations during the sessions; *Group* showed no significant main or interaction effects (*Group*: $F(6, 404)=1.102$, $p=.360$, Wilk's $\Lambda=0.983$; *Group*×*Session* interaction: $F(12, 808)=0.671$, $p=.780$, Wilk's $\Lambda=0.980$; *Group*×*Time* interaction: $F(6, 404)=0.496$, $p=.811$, Wilk's $\Lambda=0.993$). For tDCS side effect scores, *Group* showed a significant main effect ($F(11, 196)=2.219$, $p=.015$, Wilk's $\Lambda=0.889$). The real versus sham tDCS group showed numerically higher scores for burning and itching sensations. However, no significant group differences were found when the side effects were tested separately in a Wilcoxon-Mann-Whitney test (p's>.145).

Table S2.1.1. Emotional state and tDCS side effect ratings, averaged over sessions.

	Pre-session				Post-session			
	Real tDCS		Sham tDCS		Real tDCS		Sham tDCS	
Item	mean	SD	mean	SD	mean	SD	mean	SD
STAI-6: calm	3.37	0.69	3.39	0.69	3.25	0.69	3.14	0.79
STAI-6: tense	1.24	0.53	1.32	0.60	1.23	0.50	1.35	0.56
STAI-6: upset	1.04	0.23	1.01	0.10	1.15	0.41	1.20	0.49
STAI-6:relaxed	3.21	0.72	3.25	0.66	3.10	0.70	3.10	0.74
STAI-6:content	3.29	0.58	3.26	0.58	2.91	0.76	2.93	0.75
STAI-6: worried	1.17	0.40	1.23	0.51	1.14	0.38	1.20	0.49
tDCS: acute change in mood					1.05	0.23	1.11	0.34
tDCS: burning					1.35	0.52	1.19	0.42
tDCS: concentration problems					1.41	0.72	1.35	0.65
tDCS: dizzy					1.03	0.16	1.04	0.20
tDCS: drowsy					1.21	0.56	1.18	0.48
tDCS: headache					1.10	0.38	1.11	0.34
tDCS: itching					1.42	0.61	1.25	0.52
tDCS: nausea					1.02	0.13	1.00	0.00
tDCS: neck_pain					1.03	0.16	1.03	0.17
tDCS: pain on skull					1.08	0.33	1.02	0.14
tDCS: tingling					1.33	0.51	1.27	0.51
tDCS: intensity rating (1-100)					21.41	21.82	14.81	15.45
tDCS: comfort rating (1-100)					70.37	26.43	73.29	29.30

EMOTIONAL WORKING MEMORY TRAINING

Table S2.2.1. Model output from full GLMM of emotional *N*-Back training performance.

Random factors:	**Variance**	**SD**	
Variance of random intercept for Participant	4.68E-02	0.22	
Variance of random slope for Block by Participant	2.44E-03	4.94E-02	
Residual	0.10	0.32	
Fixed factors:	***b***	**SE**	***p***
(Intercept)	2.16	0.13	<.001
Group	0.22	0.19	.228
Session 2 (vs. 1)	0.63	5.60E-02	<.001
Session 3 (vs. 1)	1.17	6.34E-02	<.001
Block	24.11	2.75	<.001
Block^2	-3.32	1.26	.009
Group x Session 2 (vs. 1)	-7.34E-02	7.79E-02	.345
Group x Session 3 (vs. 1)	-0.45	8.54E-02	<.001
Group x Block	0.47	3.74	.900
Group x Block^2	-4.57	1.87	.015
Session 2 (vs. 1) x Block	-0.25	2.44	.920
Session 3 (vs. 1) x Block	-3.82	2.85	.180
Session 2 (vs. 1) x Block^2	-4.45	2.34	.057
Session 3 (vs. 1) x Block^2	-3.90	2.74	.155
Group x Session 2 (vs. 1) x Block	-3.26	3.37	.333
Group x Session 3 (vs. 1) x Block	-1.34	3.74	.721
Group x Session 2 (vs. 1) x Block^2	3.76	3.37	.265
Group x Session 3 (vs. 1) x Block^2	-0.21	3.66	.954

Formula: WM-load-level ~ Group * Session * (Block, Block^2) + (1|Participant) + (0+Block|Participant)

Effects of online versus offline tDCS on N-Back training performance

To explore whether online versus offline tDCS differentially influenced *N*-Back performance, the GLMM was repeated separately for *N*-Back training performance during blocks 1-5 (first 10 minutes of the task, while tDCS was turned on) and for performance during blocks 6-10 (second 10 minutes of the task, while tDCS was turned off). The results are reported in **Table S2.2.1.1.** The results were not significantly different from the results of the GLMM analyzing total task performance, suggesting no significant differences in the effects of online versus offline tDCS.

Table S2.2.1.1. Model output from full GLMM of emotional *N*-Back training performance separately for online tDCS (blocks 1-5) and offline tDCS (blocks 6-10).

	***N*-Back blocks 1-5 (online tDCS)**			***N*-Back blocks 6-10 (offline tDCS)**		
Fixed factors:	***b***	**SE**	***p***	***b***	**SE**	***p***
(Intercept)	*1.75*	*0.12*	*0.000*	*2.60*	*0.18*	*0.000*
Group	0.17	0.16	0.295	0.23	0.26	0.374
Session 2 (vs. 1)	0.62	0.07	0.000	0.63	0.09	0.000
Session 3 (vs. 1)	1.21	0.08	0.000	1.10	0.10	0.000
Block	13.03	1.85	0.000	5.66	1.92	0.003
Block^2	-0.99	1.09	0.363	3.50	1.57	0.026
Group x Session 2 (vs. 1)	0.03	0.09	0.749	-0.17	0.12	0.145
Group x Session 3 (vs. 1)	-0.32	0.11	0.003	-0.55	0.13	0.000
Group x Block	2.48	2.51	0.322	-3.24	2.55	0.203
Group x Block^2	-0.29	1.60	0.857	-4.10	2.31	0.075
Session 2 (vs. 1) x Block	0.68	1.98	0.732	-0.83	2.78	0.765
Session 3 (vs. 1) x Block	-1.84	2.47	0.458	-2.40	3.04	0.431
Session 2 (vs. 1) x Block^2	-4.70	1.94	0.015	-4.05	2.69	0.132
Session 3 (vs. 1) x Block^2	-4.96	2.41	0.040	-5.07	2.95	0.086
Group x Session 2 (vs. 1) x Block	-2.21	2.87	0.441	1.69	3.84	0.660
Group x Session 3 (vs. 1) x Block	4.03	3.37	0.231	0.69	4.08	0.866
Group x Session 2 (vs. 1) x Block^2	0.42	2.83	0.881	2.60	3.75	0.488
Group x Session 3 (vs. 1) x Block^2	1.16	3.29	0.726	7.01	4.02	0.081

Formula: WM-load-level ~ Group * Session * (Block, Block^2) + (1|Participant) + (0+Block|Participant)

Table S2.2.2. Model output from GLMMs per session with emotional *N*-Back training performance as outcome variable.

	Session 1			Session 2			Session 3		
Random factors:	**Variance**	**SD**		**Variance**	**SD**		**Variance**	**SD**	
Variance of random intercept for Participant	7.72E-03	8.79E-02		0.17	0.42		0.24	0.49	
Variance of random slope for Block by Participant	4.64E-03	6.81E-02		4.32E-03	6.57E-02		4.86E-03	6.97E-02	
Residual	9.70E-02	0.31		8.23E-02	0.29		7.79E-02	0.28	
Fixed factors:	***b***	**SE**	***p***	***b***	**SE**	***p***	***b***	**SE**	***p***
(Intercept)	2.08	0.13	<.001	2.97	0.20	<.001	3.42	0.23	<.001
Group	0.23	0.18	.194	6.91E-02	0.28	.803	-0.17	0.32	.603
Block	14.31	1.90	<.001	15.33	1.83	<.001	11.43	1.95	<.001
Block^2	-2.68	0.69	<.001	-3.47	0.88	<.001	-4.29	1.14	<.001
Group x Block	1.92	2.58	.457	-4.03	2.45	.100	-3.76E-02	2.66	.989
Group x Block^2	-1.93	1.01	.058	-1.45	1.27	.253	-2.80	1.46	.055

Formula: WM-load-level ~ Group * (Block, Block^2) + (1|Participant) + (0+Block|Participant)

Table S2.2.3. Estimated marginal means contrasts between tDCS groups (real–sham).

Session	Estimated marginal means difference	SE	*p*	*d*
1	0.34	0.19	.081	1.05
2	0.17	0.20	.404	0.53
3	-0.11	0.21	.616	0.33

POST-ASSESSMENT EMOTIONAL WORKING MEMORY TEST

Table S2.3.1. Model output from full GLMMs of *N*-Back test RT and sensitivity (*d'*).

	RT			***d'***		
Random factors:	**Variance**	**SD**		**Variance**	**SD**	
Variance of random intercept for Participant	1101.22	105.36		9.02E-02	0.30	
Variance of random slope for Load by Participant	986.30	31.41		2.03E-03	4.51E-02	
Residual	1.35E-02	0.12		1.98E-03	4.45E-02	
Fixed factors:	***b***	**SE**	***p***	***b***	**SE**	***p***
(intercept)	1023.26	99.10	<.001	2.12	0.30	<.001
Train max.	-53.83	21.90	.014	0.31	6.55E-02	<.001
Group	9.37	35.52	.792	-0.12	0.13	.366
Load	49.44	7.72	<.001	-0.71	2.68E-02	<.001
Group * Load	-10.72	10.25	.296	2.32E-02	3.79E-02	.541

Formulas:
RT ~ Train max. + Group * Session + (1|Participant) + (0+Load|Participant)
d' ~ Train max. + Group * Session + (1|Participant) + (0+Load|Participant)

NPU-THREAT TEST

NPU-threat test: Testing the threat manipulation.

Tables S.2.4.1. and **S2.4.2.** show that startle amplitudes and fear ratings were significantly higher in the Predictable- and Unpredictable-shock conditions compared to the No-shock condition. Startle amplitudes were also significantly higher in the Predictable- compared to the Unpredictable-shock condition, while the fear ratings were higher in the Unpredictable-shock condition (during the ITI context). Moreover, in the Predictable-shock condition, startle amplitudes and fear ratings were higher during Cue than during ITI. These effects confirm the intended threat manipulations. Moreover, significant negative effects of *Sequence* and *Probe number* indicate a decrease in threat responding over time, presumably reflecting habituation.

Table S2.4.1. Model output from full GLMMs testing the threat manipulation on startle amplitudes and fear ratings.

	Startle amplitudes			Fear ratings		
Random factors:	**Variance**	**SD**		**Variance**	**SD**	
Variance of random intercept for Participant	*NA*			6.62E-04	2.57E-02	
Variance of random slope for Probe no. by Participant	8.05E-05	8.97E-03		*NA*		
Residual	0.19	0.44		7.50E-02	0.27	
Fixed Factors:	***b***	**SE**	***p***	***b***	**SE**	***p***
(intercept)	1.90	3.05E-02	<.001	2.27	2.97E-02	<.001
Probe No.	-6.36E-02	7.54E-03	<.001	*NA*		
Sequence	-0.38	4.31E-02	<.001	-0.19	4.00E-02	<.001
Condition P (vs. N)	0.85	5.17E-02	<.001	0.93	5.00E-02	<.001
Condition U (vs. N)	0.79	5.10E-02	<.001	1.28	5.40E-02	<.001
Context	-4.00E-02	4.31E-02	.354	-2.32E-02	4.00E-02	.561
Probe No. * Sequence	3.90E-02	1.05E-02	<.001	*NA*		
Probe No. * Condition P (vs. N)	-9.31E-02	1.22E-02	<.001	*NA*		
Probe No. * Condition U (vs. N)	-8.95E-02	1.20E-02	<.001	*NA*		
Sequence * Condition P (vs. N)	-0.18	7.31E-02	.014	-3.39E-02	6.91E-02	.623
Sequence * Condition U (vs. N)	-4.31E-02	7.22E-02	.551	-6.71E-02	7.41E-02	.365
Probe No. * Context	-9.44E-03	1.04E-02	.366	*NA*		
Sequence * Context	2.97E-02	6.10E-02	.627	1.85E-02	5.65E-02	.744
Condition P (vs. N) * Context	-0.23	7.31E-02	.001	-0.27	6.91E-02	<.001
Condition U (vs. N) * Context	5.10E-02	7.22E-02	.480	-3.60E-02	7.41E-02	.627
Probe*Sequence*Condition P (vs. N)	1.81E-02	1.72E-02	.292	*NA*		
Probe*Sequence*Condition U (vs. N)	-1.52E-02	1.70E-02	.372	*NA*		
Probe*Sequence*Context	-4.81E-03	1.48E-02	.745	*NA*		
Probe*Condition P (vs. N)*Context	4.06E-04	1.72E-02	.981	*NA*		
Probe*Condition U (vs. N)*Context	1.33E-04	1.70E-02	.994	*NA*		
Sequence*Condition P (vs. N)*Context	-4.02E-02	0.10	.697	-7.71E-02	9.77E-02	.430
Sequence*Condition U (vs. N)*Context	-0.13	0.10	.203	1.10E-02	0.11	.916
Probe*Sequence*Condition P (vs. N)* Context	2.89E-02	2.43E-02	.235	*NA*		
Probe*Sequence*Condition U (vs. N)* Context	2.32E-02	2.40E-02	.334	*NA*		

Formulas:
Startle amplitude ~ Probe no. * Sequence * Condition * Context + (0+Probe no.|Participant)
Fear rating ~ Sequence * Condition * Context + (1| Participant)

■ **Table S2.4.2.** Estimated marginal means: contrasts between conditions and contexts.

Contrast conditions		**Cue**				**ITI**			
Contrast	**Sequence**	**Estimated marginal means difference**	**SE**	***p***	***d***	**Estimated marginal means difference**	**SE**	***p***	***d***
Startle amplitudes									
N - P	1	-0.80	5.07E-02	<.001	1.83	-0.41	4.36E-02	<.001	0.93
N - U	1	-0.48	4.71E-02	<.001	1.10	-0.60	4.59E-02	<.001	1.38
P - U	1	0.32	5.55E-02	<.001	0.73	-0.20	5.01E-02	<.001	0.45
N - P	2	-0.57	3.99E-02	<.001	1.31	-0.30	3.47E-02	<.001	0.70
N - U	2	-0.39	3.79E-02	<.001	0.90	-0.42	3.63E-02	<.001	0.96
P - U	2	0.18	4.39E-02	<.001	0.41	-0.11	3.93E-02	.012	0.26
Fear ratings									
N - P	1	-1.10	0.11	<.001	4.03	-0.80	9.94E-02	<.001	2.93
N - U	1	-1.35	0.11	<.001	4.94	-1.29	0.11	<.001	4.18
P - U	1	-0.25	0.13	.127	0.91	-0.49	0.12	<.001	1.79
N - P	2	-1.13	9.77E-02	<.001	4.14	-0.68	8.78E-02	<.001	2.47
N - U	2	-1.25	0.10	<.001	4.56	-1.21	9.89E-02	<.001	4.41
P - U	2	-0.12	0.12	.585	0.42	-0.53	0.11	<.001	1.94
Contrast contexts		**Predictable shock**				**Unpredictable shock**			
Contrast	**Sequence**	**Estimated marginal means difference**	**SE**	***p***	***d***	**Estimated marginal means difference**	**SE**	***p***	***d***
Startle amplitudes									
Cue-ITI	1	0.51	5.35E-02	<.001	1.17	4.44E-03	5.21E-02	.932	0.01
Cue-ITI	2	0.36	4.19E-02	<.001	0.82	6.64E-02	4.14E-02	.109	0.15
Fear ratings									
Cue-ITI	1	0.35	0.12	.003	1.29	0.11	0.13	.389	0.41
Cue-ITI	2	0.47	0.11	<.001	1.71	5.43E-02	0.12	.645	0.20

NPU-threat test: Testing effects of Time and tDCS Group.

Table S2.4.3. Model output from full GLMMs testing effects of *Time* and *tDCS Group* on startle amplitudes and fear ratings.

	Startle amplitudes			Fear ratings		
Random factors:	**Variance**	**SD**		**Variance**	**SD**	
Variance of random intercept for Participant	*NA*			6.62E-04	2.57E-02	
Variance of random slope of Probe no. by Participant	6.93E-04	2.63E-02		*NA*		
Residual	0.19	0.43		7.50E-02	0.27	
Fixed factors:	***b***	**SE**	***p***	***b***	**SE**	***p***
(intercept)	2.81	4.36E-02	<.001	3.76	7.14E-02	<.001
Probe no.	-0.15	1.13E-02	<.001	*NA*		
Sequence	-0.46	6.17E-02	<.001	-0.34	7.34E-02	<.001
Group	-4.92E-02	6.16E-02	.424	0.15	0.10	.125
Time	-0.13	6.17E-02	.038	-0.53	6.95E-02	<.001
Condition P vs. U	-0.19	6.16E-02	<.001	0.18	7.31E-02	.014
Probe no. * Sequence	2.84E-02	1.44E-02	.049	*NA*		
Probe no. * Group	2.83E-02	1.59E-02	.074	*NA*		
Sequence * Group	-5.84E-02	8.72E-02	.503	0.18	0.10	.081
Probe no. * Time	6.78E-03	1.44E-02	.638	*NA*		
Sequence * Time	0.11	8.72E-02	.223	0.19	9.65E-02	.045
Group * Time	-0.18	8.72E-02	.037	-0.32	9.81E-02	.001
Probe no. * Condition	5.27E-03	1.44E-02	.715	*NA*		
Sequence * Condition	0.13	8.72E-02	.142	-0.14	0.10	.184
Group * Condition	6.40E-04	8.72E-02	.994	-0.12	0.10	.263
Time * Condition	-3.83E-02	8.72E-02	.660	-0.11	9.60E-02	.248
Probe no. * Sequence * Group	1.14E-02	2.04E-02	.575	*NA*		
Probe no. * Sequence * Time	-1.94E-02	2.04E-02	.342	*NA*		
Probe no. * Group * Time	1.76E-02	2.04E-02	.388	*NA*		
Sequence * Group * Time	-1.29E-02	0.12	.917	-8.28E-02	0.14	.544
Probe * Sequence * Condition	-1.61E-02	2.04E-02	.430	*NA*		
Probe * Group * Condition	-1.48E-02	2.04E-02	.468	*NA*		
Sequence * Group * Condition	-5.54E-02	0.12	.653	0.14	0.15	.339
Probe * Time * Condition	1.04E-02	2.04E-02	.609	*NA*		
Sequence * Time * Condition	0.24	0.12	.049	0.14	0.14	.285
Group * Time * Condition	-6.41E-03	0.12	.959	8.80E-02	0.14	.517
Probe * Sequence * Group * Time	-1.58E-02	2.88E-02	.583	*NA*		

■ **Table S2.4.3.** (Continued)

	Startle amplitudes			Fear ratings		
Fixed factors:	***b***	**SE**	***p***	***b***	**SE**	***p***
Probe*Sequence*Group* Condition	2.97E-02	2.88E-02	.303	*NA*		
Probe*Sequence*Time* Condition	-5.83E-02	2.88E-02	.043	*NA*		
Probe*Group*Time* Condition	1.21E-02	2.88E-02	.673	*NA*		
Sequence*Group*Time* Condition	3.22E-02	0.17	.854	-0.13	0.19	.505
Probe*Sequence*Group* Time*Condition	-3.99E-03	4.08E-02	.922	*NA*		

Formulas:
Startle amplitude ~ Time * Group * Probe no. * Sequence * Condition + (0+Probe no.|Participant)
Fear rating. ~ Time * Group * Sequence * Condition + (1| Participant)

■ **Table S2.4.4.** Estimated marginal means contrasts between tDCS groups (real–sham).

		Predictable shock				Unpredictable shock			
Time	**Sequence**	**Estimated marginal means difference**	**SE**	***p***	***d***	**Estimated marginal means difference**	**SE**	***p***	***d***
Startle amplitudes									
Baseline	1	0.27	0.13	.035	0.61	5.69E-02	0.12	.625	0.13
	2	0.27	0.10	.007	0.63	0.17	9.35E-02	.067	0.40
Post	1	8.93E-02	0.12	.464	0.21	-5.09E-02	0.11	.631	0.12
	2	-0.13	9.46E-02	.161	0.31	-9.57E-02	8.94E-02	.284	0.22
Fear ratings									
Baseline	1	0.25	0.23	.278	1.19	-0.18	0.25	.474	0.85
	2	0.42	0.21	.050	1.98	0.38	0.22	.081	1.81
Post	1	-0.30	0.20	.142	1.43	-0.37	0.21	.075	1.77
	2	-0.12	0.19	.539	0.57	-0.16	0.20	.426	0.75

EXPLORATORY ANALYSIS OF PREDICTORS

Table S2.5.1. Model output from full GLMMs of emotional *N*-Back training performance, including predictor *Theta/beta Ratio*.

Fixed effects	***b***	**SE**	***p***
(Intercept)	1.56	0.14	<.001
Group	0.42	0.20	.034
Session	0.61	0.03	<.001
Block	27.36	3.59	<.001
Block^2	0.20	2.39	.934
Theta/beta ratio	-0.04	0.16	.802
Group * Session	-0.23	0.04	<.001
Group * Block	-0.11	4.80	.982
Group * Block^2	-6.31	3.37	.061
Session * Block	-2.07	1.47	.160
Session * Block^2	-2.81	1.37	.040
Theta/beta ratio * Group	0.39	0.20	.055
Theta/beta ratio * Session	0.07	0.03	.035
Theta/beta ratio * Block	5.74	3.72	.123
Theta/beta ratio * Block^2	2.90	2.41	.228
Group * Session * Block	-1.34	1.93	.489
Group * Session * Block^2	1.01	1.85	.587
Group * Session * Theta/beta ratio	-0.11	0.04	.013
Group * Block * Theta/beta ratio	2.14	4.70	.649
Group * Block^2 * Theta/beta ratio	-8.76	3.19	.006
Session * Block * Theta/beta ratio	-1.85	1.41	.190
Session * Block^2 * Theta/beta ratio	-0.30	1.41	.829
Group * Session * Block * Theta/beta ratio	-0.90	1.79	.615
Group * Session * Block^2 * Theta/beta ratio	2.78	1.77	.117

Formula:
WM-load-level ~ Theta/beta Ratio * Group * Session * (Block, Block^2) + (1|Participant) + (0+Block|Participant)
Interaction terms of interest (interactions between *Group*, a time variable like *Session* or *Block*, and *Theta/beta Ratio*) are printed in **bold**.

Table S2.5.2. Model output from full GLMMs of emotional *N*-Back training performance, including predictors *Education, Age* and *Start Performance*.

Fixed effects	***b***	**SE**	***p***
(Intercept)	1.01	0.29	<.001
Group	0.67	0.42	.113
Session	0.51	0.07	<.001
Block	12.33	8.03	.124
Block^2	6.06	5.35	.257
Age	-0.02	0.12	.839
Education	0.08	0.09	.351
Start performance	0.18	0.12	.135
Group * Session	-0.21	0.10	.043
Group * Block	10.75	11.40	.346
Group * Block^2	-2.31	8.44	.784
Session * Block	2.95	3.18	.354
Session * Block^2	-5.23	3.07	.088
Group * Education	-0.22	0.13	.085
Session * Education	0.05	0.03	.060
Block * Education	5.86	2.81	.037
Block^2 * Education	-0.55	2.09	.791
Group * Age	-0.02	0.17	.900
Session * Age	-0.10	0.03	<.001
Block * Age	-5.09	3.26	.118
Block^2 * Age	-1.22	2.16	.574
Group * Start performance	0.33	0.17	.056
Session * Start performance	-0.01	0.03	.721
Block * Start performance	-1.44	3.52	.682
Block^2 * Start performance	-6.39	2.53	.012
Group * Session * Block	-5.33	4.45	.231
Group * Session * Block^2	-1.74	4.57	.704
Group * Session * Education	0.04	0.04	.302
Group * Block * Education	-8.86	3.77	.019
Group * Block^2 * Education	-1.33	2.90	.646
Session * Block * Education	-2.51	1.21	.038
Session * Block^2 * Education	-0.20	1.14	.860
Group * Session * Age	-0.04	0.04	.334
Group * Block * Age	6.49	4.91	.186
Group * Block^2 * Age	7.88	3.41	.021
Session * Block * Age	2.25	1.31	.085

■ **Table S2.5.2.** (Continued).

Fixed effects	***b***	**SE**	***p***
Session * Block² * Age	1.91	1.20	.112
Group * Session * Start performance	-0.12	0.05	.009
Group * Block * Start performance	12.44	4.97	.012
Group * Block² * Start performance	0.11	3.71	.977
Session * Block * Start performance	1.33	1.45	.359
Session * Block² * Start performance	3.07	1.40	.028
Group * Session * Block * Education	4.27	1.56	.006
Group * Session * Block² * Education	1.15	1.54	.454
Group * Session * Block * Age	-5.16	1.91	.007
Group * Session * Block² * Age	-4.97	1.81	.006
Group * Session * Block * Start performance	-6.67	2.00	.001
Group * Session * Block² * Start performance	0.16	1.98	.936

Formula:
WM-load-level ~ Age * Group * Session * (Block, Block²) + Education * Group * Session * (Block, Block²) + Start performance * Group * Session * (Block, Block²) + (1|Participant) + (0+Block|Participant)
Interaction terms of interest (interactions between *Group*, a time variable like *Session* or *Block*, and a predictor variable) are printed in **bold**.

Table S2.5.3. Estimated marginal means of group contrasts (real–sham) per median-split subsample per predictor variable.

		Below-median subsamples				Above-median subsamples			
Session	**Predictor variable**	**Estimated marginal mean difference**	**SE**	***p***	***d***	**Estimated marginal mean difference**	**SE**	***p***	***d***
1	Theta/beta Ratio	-0.24	0.28	.402	0.75	0.84	0.28	.002	2.65
	Age	0.73	0.20	<.001	2.37	-0.14	0.20	.489	0.44
	Education	0.58	0.23	.013	1.76	-0.12	0.31	.691	0.38
	Start Performance	0.06	0.24	.813	0.18	0.72	0.25	.004	2.28
2	Theta/beta Ratio	-0.12	0.30	.693	0.37	0.34	0.29	.237	1.09
	Age	0.14	0.31	.663	0.44	-0.04	0.32	.901	0.13
	Education	0.36	0.25	.145	1.10	-0.34	0.34	.318	1.04
	Start Performance	0.05	0.26	.844	0.16	0.27	0.27	.311	0.86
3	Theta/beta Ratio	-0.26	0.30	.384	0.84	-0.13	0.30	.661	0.42
	Age	-0.11	0.34	.749	0.35	-0.32	0.35	.360	1.03
	Education	0.02	0.26	.948	0.05	-0.38	0.36	.292	1.15
	Start Performance	-0.15	0.27	.573	0.47	-0.16	0.28	.558	0.51

REFERENCES

1. Sheehan D v., Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. In: *Journal of Clinical Psychiatry*. Vol 59. ; 1998:22-33. doi:10.1016/S0924-9338(99)80239-9

2. Feeser M, Prehn K, Kazzer P, Mungee A, Bajbouj M. Transcranial Direct Current Stimulation Enhances Cognitive Control During Emotion Regulation. *Brain Stimulation*. 2014;7(1):105-112. doi:10.1016/j.brs.2013.08.006

3. He Z, Lin Y, Xia L, Liu Z, Zhang D, Elliott R. Critical role of the right VLPFC in emotional regulation of social exclusion: A tDCS study. *Social Cognitive and Affective Neuroscience*. 2018;13(4):357-366. doi:10.1093/scan/nsy026

4. Marques LM, Morello LYN, Boggio PS. Ventrolateral but not Dorsolateral Prefrontal Cortex tDCS effectively impact emotion reappraisal – effects on Emotional Experience and Interbeat Interval. *Scientific Reports*. 2018;8(1):15295. doi:10.1038/s41598-018-33711-5

5. Herrmann MJ, Beier JS, Simons B, Polak T. Transcranial Direct Current Stimulation (tDCS) of the Right Inferior Frontal Gyrus Attenuates Skin Conductance Responses to Unpredictable Threat Conditions. *Frontiers in Human Neuroscience*. 2016;10(July):1-6. doi:10.3389/fnhum.2016.00352

6. Herrmann MJ, Simons BSE, Horst AK, Boehme S, Straube T, Polak T. Modulation of sustained fear by transcranial direct current stimulation (tDCS) of the right inferior frontal cortex (rIFC). *Biological Psychology*. 2018;139(July):173-177. doi:10.1016/j.biopsycho.2018.10.013

7. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods*. 2007;39(2):175-191. doi:10.3758/BF03193146

8. Schweizer S, Grahn J, Hampshire A, Mobbs D, Dalgleish T. Training the Emotional Brain: Improving Affective Control through Emotional Working Memory Training. *Journal of Neuroscience*. 2013;33(12):5301-5311. doi:10.1523/JNEUROSCI.2593-12.2013

9. Schmitz A, Grillon C. Assessing fear and anxiety in humans using the threat of predictable and unpredictable aversive events (the NPU-threat test). *Nature Protocols*. 2012;7(3):527-532. doi:10.1038/nprot.2012.001

10. Shurick AA, Hamilton JR, Harris LT, Roy AK, Gross JJ, Phelps EA. Durable effects of cognitive restructuring on conditioned fear. *Emotion*. 2012;12(6):1393-1397. doi:10.1037/a0029143

11. Eippert F, Veit R, Weiskopf N, Erb M, Birbaumer N, Anders S. Regulation of emotional responses elicited by threat-related stimuli. *Human Brain Mapping*. 2007;28(5):409-423. doi:10.1002/hbm.20291

12. Raio CM, Orederu TA, Palazzolo L, Shurick AA, Phelps EA. Cognitive emotion regulation fails the stress test. *Proceedings of the National Academy of Sciences*. 2013;110(37):15139-15144. doi:10.1073/pnas.1305706110

13. Denny BT, Ochsner KN. Behavioral effects of longitudinal training in cognitive reappraisal. *Emotion*. 2014;14(2):425-433. doi:10.1037/a0035276

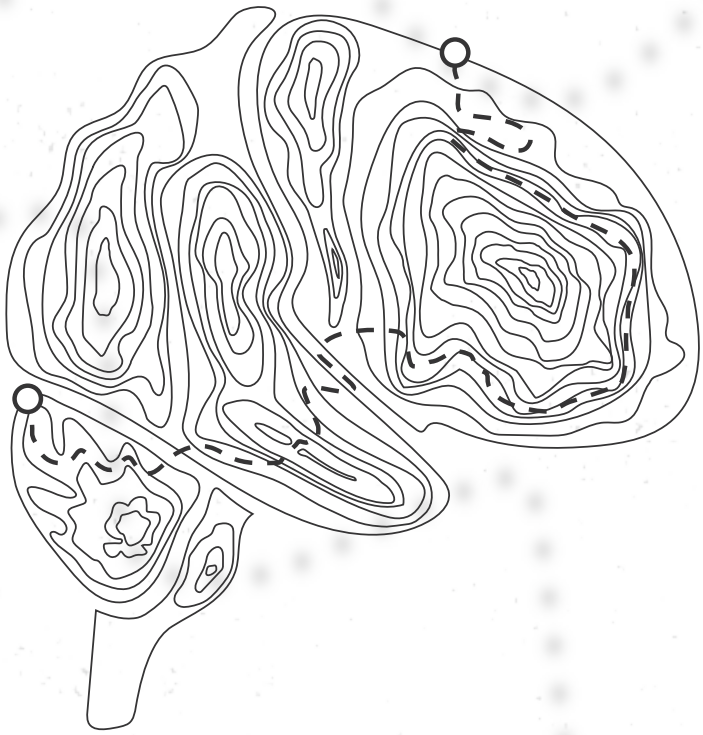
14. Blumenthal TD, Cuthbert BN, Filion DL, Hackley S, Lipp O v., van Boxtel A. Committee report: Guidelines for human startle eyeblink electromyographic studies. *Psychophysiology*. 2005;42(1):1-15. doi:10.1111/j.1469-8986.2005.00271.x

15. Bradford DE, Magruder KP, Korhumel RA, Curtin JJ. Using the Threat Probability Task to Assess Anxiety and Fear During Uncertain and Certain Threat. *Journal of Visualized Experiments*. 2014;(91). doi:10.3791/51905

16. Delorme A, Makeig S. *EEGLAB: An Open Source Toolbox for Analysis of Single-Trial EEG Dynamics Including Independent Component Analysis*. Vol 134.; 2004. Accessed March 30, 2021. http://www.sccn.ucsd.edu/eeglab/

17. Lopez-Calderon J, Luck SJ. ERPLAB: an open-source toolbox for the analysis of event-related potentials. *Frontiers in Human Neuroscience*. 2014;8(1 APR):213. doi:10.3389/fnhum.2014.00213

18. Heesink L, Kleber R, Häfner M, van Bedaf L, Eekhout I, Geuze E. Anger and aggression problems in veterans are associated with an increased acoustic startle reflex. *Biological Psychology*. 2017;123:119-125. doi:10.1016/j.biopsycho.2016.12.004



CHAPTER 6

No effects on cognitive control following multisession transcranial direct current stimulation combined with working memory training in healthy military personnel

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Unpublished manuscript ■

ABSTRACT

Background: Goal-directed behavior and psychological resilience in stressful circumstances require high levels of cognitive control. Prior studies have shown beneficial effects of transcranial direct current stimulation (tDCS) combined with cognitive training on aspects of cognitive control, but the duration and generalization of such effects remain unclear. The aim of the present study was to investigate the behavioral and electrophysiological effects of multisession tDCS over the dorsolateral prefrontal cortex (DLPFC) combined with working memory training on aspects of cognitive control in military personnel.

Methods: In a double-blind between-subjects randomized controlled trial, healthy military servicemembers (N=76, 18-60 years) underwent three sessions of real or sham anodal tDCS over the right DLPFC (2 mA, 20 minutes) combined with an emotional *N*-back training. Cognitive control was assessed by emotional Go/No-go task performance and self-reported attentional control. In addition, electrophysiological correlates of cognitive control were indexed by the N2 and P3 waves in Go/No-go task event-related potentials and resting-state frontal alpha asymmetry. The outcome variables were assessed within 1-6 days before and after the tDCS-training intervention.

Results. No significant effects were observed in behavioral or electrophysiological indices of cognitive control after the tDCS-working memory training intervention.

Conclusions. Our findings do not support the effectivity of multisession tDCS combined with *N*-back training on cognitive control in healthy military personnel. These results emphasize the need to better understand the conditions by which tDCS can sort reliable neuroplastic effects on cognitive control circuits.

INTRODUCTION

For military personnel operating in extreme or threatening environments, 'keeping a cool head' can be a matter of life and death. Operating in these environments can be challenging and stressful, and may negatively impact both operational performance and mental health[1–5]. An essential aspect of psychological resilience in such circumstances is adequately adapting to the stressful and changing contexts[6]. This process involves coordinating and adjusting your thoughts and actions in a context-appropriate way to maintain goal-directed behavior, and is also referred to as 'cognitive control'[7]. Improving cognitive control could thus promote psychological resilience in military servicemembers[8–10].

Several executive functions play an important role in cognitive control, including working memory, attentional control and inhibitory control[7]. Working memory provides a space in mind to maintain task goals and manipulate information to allow for selection of context-appropriate actions. Attentional control is needed to regulate attentional focus or shifting between relevant information. Inhibitory control is needed to suppress interference of irrelevant information and withhold context-inappropriate reactions. Interestingly, these three executive functions activate partly overlapping brain regions, in support of a so-called cognitive control brain network[11]. Several of those regions, including the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC), are likewise implicated in processes relevant to psychological resilience such as top-down regulation of emotions[12]. Reinforcing the function of this network may provide a way to improve cognitive control.

Hubs of the cognitive control network can be targeted with non-invasive brain stimulation techniques such as transcranial direct current stimulation (tDCS)[13]. With tDCS, a low-intensity electrical current (usually 1-2.5 mA) is applied between electrodes on the scalp, which can modulate neural excitability in superficial cortical layers[14]. While the polarity-dependent effects of tDCS depend on many factors, cortical excitability is assumed to increased following anodal tDCS and decrease following cathodal tDCS[15]. Meta-analytic evidence from tDCS research in healthy volunteers supports that single-session anodal tDCS over the DLPFC can improve performance and influence neurophysiological markers of several important aspects of working memory, attentional processes and inhibitory control[16–19]. However, effects of single-session tDCS have been shown to fade after several hours[20] and effects on cognitive task performance are variable[21]. Multiple (typically 2-10) tDCS sessions combined with cognitive training have shown more consistent and longer-lasting benefits on cognitive performance[22]. Interestingly, some studies showed that tDCS-related improvements of cognitive performance generalize to other non-trained cognitive functions that presumably depend on shared underlying processes[23–27].

In a recent study, we applied multisession anodal tDCS over the right DLPFC combined with working memory training using an emotional *N*-Back task with the aim to improve top-down regulation of emotion in military personnel. The primary analyses of this study showed that

tDCS did not significantly influence emotion regulation, but did seem to accelerate learning during the early stages of the emotional *N*-Back training (see **Chapter 5**). While the *N*-back task predominantly recruits working memory, the task also activates elements of attentional and inhibitory control[28,29].

In addition to studying attentional and inhibition aspects of cognitive control, electroencephalography (EEG) provides a way to study neural correlates of cognitive control processes. For example, the amount of automatic attention and conflict monitoring is thought to be reflected in an early negative deflection in the event-related potential (ERP) during cognitive task performance, called the N2. Orientation of attention and performance monitoring is thought to be reflected in a later positive deflection, called the P3[30,31]. Furthermore, meta-analytic evidence supports effects of tDCS to the PFC on resting-state functional connectivity[32,33]. One resting-state EEG readout that has received much interest regarding its involvement in PFC activity and in cognitive control of approach and avoidance related motivational tendencies is the asymmetry between left versus right PFC activity[34]. Frontal asymmetry is typically based on power in the alpha band (8-12 Hz), which is assumed to be inversely related to cortical activity[35,36]. Frontal activity asymmetry has been hypothesized to reflect the balance between approach motivation and inhibitory control of behavior[37,38], in line with the significant role of the right PFC in inhibitory control[39].

The present study tested the hypothesis that the intervention of multisession tDCS to the right DLPFC combined with emotional *N*-Back training in military personnel would improve non-trained aspects of cognitive control and underlying neurophysiological mechanisms. Specifically, we hypothesized that inhibitory and attentional control performance would improve as a function of the real versus sham tDCS-training intervention, reflected by better Go/No-go performance and higher attentional self-report scores. Additionally, we hypothesized that neural correlates of inhibitory and attentional control as reflected by the Go/No-go task associated N2 and P3 ERPs would increase, while the resting-state EEG frontal activity asymmetry would decrease.

METHODS

PARTICIPANTS

Active-duty military personnel of 18-60 years of age with uncorrected normal hearing were recruited[a]. Exclusion criteria were alcohol or drug dependence, psychoactive medication or drug use within the past two weeks, (history of) psychiatric or neurological disorder (except for ADHD) or serious head trauma, large or ferromagnetic metal parts in the head, implanted cardiac pacemaker or neurostimulator, pregnancy, neurostimulation in the past month,

a. This study was part of a randomized controlled trial that was pre-registered at the Netherlands Trial Register (www.trialregister.nl) with ID NL8028.

and skin damage or diseases at intended electrode sites. The study procedures complied with the ethical standards of the relevant national and institutional committees on human experimentation and with the Declaration of Helsinki. All participants provided written informed consent and received €65 financial compensation for participation. The medical ethical committee of the University Medical Center Utrecht approved the study. Demographic and psychological characteristics per tDCS group are shown in **Table 1**.

Table 1: Participant characteristics per group (frequency or mean±standard deviation)

		Real tDCS (n=39)	Sham tDCS (n=35)
Gender	Male:	37	33
	Female:	2	2
Age (years)		34.0±10.7	36.1±11.1
Educational level[a]	Highschool diploma	2	3
	Vocational degree	20	21
	Associate's degree	2	0
	Bachelor's degree	6	4
	Master's degree	7	7
Number of deployments	Never deployed:	16	11
	1 deployment:	6	8
	2-3 deployments:	8	9
	≥4 deployments:	6	7
Rank[b]	Officer:	8	6
	Student-officer:	3	3
	Senior NCO:	17	20
	Junior NCO:	9	6
Handedness[c]	Right-handed:	33	30
	Left-handed:	4	4
	No preference:	0	1
Attentional Control	Focusing:	2.7±0.4	2.6±0.5
ACS scores (rating 1-4)	Shifting:	2.8±0.3	2.8±0.4
Days between tDCS-training sessions	1 day	45 (58%)	34 (49%)
(total, all sessions)	2 days	12 (15%)	8 (11%)
	3 days	6 (8%)	9 (13%)
	4 days	9 (12%)	5 (7%)
	5 days	3 (4%)	10 (14%)
	6 days	3 (4%)	4 (6%)

[a]: Educational levels were assessed based on the Dutch educational system and for international interpretability converted to the best corresponding American degree. [b]: NCO = non-commissioned officer. [c]: Participants were asked to identify themselves as left-handed, right-handed or no preference. ACS: Attentional control scale.

NON-INVASIVE BRAIN STIMULATION AND WORKING MEMORY TRAINING

Participants underwent three tDCS sessions. TDCS was applied with a DC-stimulator Plus (NeuroConn GmbH, Ilmenau, Germany) for 20 minutes at an intensity of 2 mA with a 3x3 cm

saline-soaked sponge-covered anode placed over EEG position F4 and a 5x7 cm cathode placed lateral of C2. Sham tDCS consisted of a 16-second fade-in-fade-out stimulation at the start and end of the stimulation period. After the first 10 minutes of tDCS, the emotional *N*-back training started. This task is described in detail elsewhere (see **Chapter 5**). Briefly, each trial presented a visuospatial stimulus (angry faces in a 4x4 grid) and an auditory stimulus (negative-valanced word, e.g., "death", "fear"). Participants indicated whether either or both stimuli matched with *N* trials back. Per session, the *N*-back training task contained 10 blocks with 20+*N* trials (6 target trials), and lasted for approximately 20 minutes. The level of *N* was adaptive as the *N* was automatically adjusted to the participant's response accuracy after each block.

EEG RECORDING

Raw EEG was recorded during the whole session and amplified with a BioSemi ActiveTwo system (BioSemi B.V., Amsterdam, the Netherlands) at 2048 Hz, with 32 Ag/AgCl pin electrodes, relative to a Common Mode Sense (CMS) active electrode in combination with a Driven Right Leg (DRL) passive electrode attached to the scalp. Data from 30 EEG channels (Fp1, Fp2, AF3, AF4, F7, F8, F3, F4, Fz, Cz, FC1, FC2, FC5, FC6, C3, C4, CP1, CP2, CP5, CP6, P7, P8, P3, P4, Pz, PO3, PO4, O1, O2, Oz) were pre-processed offline with custom Matlab scripts using EEGLAB v2021.0[40] and ERPLAB v8.10[41]. Bad channels were interpolated with spherical interpolation using the *interp* function in EEGLAB. All EEG data were re-referenced to an average reference, down sampled to 256 Hz, and bandpass filtered between 0.5–30 Hz (8^{th} order, -48 dB rolloff) infinite impulse response (IIR) Butterworth filter. To control for eye movements, electrooculography (EOG) was recorded with two active 4 mm flat surface Ag/AgCl electrodes filled with conductive gel, placed in the outer canthi of the left and right eye and above and below the left eye to record horizontal and vertical eye movements.

GO/NO-GO TASK

Inhibitory control was assessed using a Go/No-go task. Participants were instructed to press the spacebar as fast as possible in response to Go-stimuli and withhold their response to No-go-stimuli. To additionally study the influence of emotional drives on inhibitory control[42], Go- and No-go stimuli were screen-filled pictures of faces with neutral or angry expressions, and presented in equal Go- and No-go-rates (50/50) to facilitate the assessment of threat-related impulsivity[43]. The emotional Go-category alternated between angry and neutral across blocks. The task consisted of six blocks (three Angry=Go blocks, three Neutral=Go blocks) with 36 trials per block. Face stimuli were presented for a maximum of 600 ms or until a response was made, alternated by variable 250-350 ms inter-trial intervals. During the baseline assessment and post-assessment, a different selection neutral and angry expressions of six female and six male faces were used from the Chicago face database[44].

Task performance

Go/No-go task performance was operationalized as the median reaction time (RT) on correct-response Go-trials and the sensitivity ($d' = z_{\text{1–omission error rate}} - z_{\text{commission error rate}}$), representing the

balance between incorrect Go-responses (omission errors) and incorrect No-go-responses (commission errors)[45].

ERPs

Continuous EEG data recorded during the Go/No-go task were segmented into epochs from -200 ms to +950 ms relative to stimulus onset, in order to capture the entire trial duration including the inter-trial interval. Epochs were then baseline-corrected to 100 ms before stimulus onset. Next, a custom script automatically marked epochs with signal fluctuations exceeding a difference of 30 μV between adjacent samples or a difference of 100 μV per 200 ms, or when the absolute amplitude of the entire epoch exceeded ±75 μV. After visual inspection, marked epochs containing artifacts due to eyeblinks or other artefacts were deleted, due to the potential contamination by movements in the average ERP. Incorrect-response trial epochs were also deleted. On average, 62±20 of the 216 epochs were deleted (29%) per individual recording. EEG datasets with less than 20 trials per condition were excluded from ERP analysis. Average ERPs were created across epochs per condition Individual N2 and P3 peak amplitudes were determined between 200-400 ms (N2) and 350–700 ms (P3) post-stimulus onset. Onset latencies were defined as the timepoint of reaching 50% of the peak amplitude[46]. Based on previous research of the topological scalp distribution of the N2 and P3 waves[30,31]), the N2 wave was averaged over channels Fz, Cz, FC1 and FC2, and the P3 wave was averaged over channels Cz, Fc1, FC2, CP1 and CP2, see also **Figure 3**.

ATTENTIONAL CONTROL SCALE

Attentional control was assessed by self-report on the Attentional Control Scale[47]. The Attentional control scale measures the ability to voluntarily focus attention (Focusing subscale) and to shift attention between tasks (Shifting subscale), and has been shown to correlate with other self-report or task-based measures of cognitive control[48]. In item 12, 'attention during lectures' was adapted to 'attention during lessons' to better fit the context of military personnel.

RESTING-STATE EEG

A 4-minute resting-state EEG was recorded at the start of the baseline and post-assessment visits. All participants received the same instruction to sit relaxed, focus on the screen (when eyes open), not to think of anything in particular, and not fall asleep. Eyes were alternatingly opened or closed for 1 minute. The cue to close or open the eyes was indicated by a beep sound. Experimenters left the room during the resting-state EEG recording.

Continuous data were segmented in 1-sec epochs. Eye blinks were identified based on the ICA function in EEGlab, and ICA components showing the eye blinks were removed from the data. Epochs were automatically marked when fluctuations in the signal exceeded a 30 μV difference between adjacent samples or a 100 μV difference per 200 ms signal, or when the absolute amplitude exceeded ±75 μV. After visual inspection, marked epochs containing artifacts due to, e.g., movement or facial muscle contractions were deleted. A fast Fourier transform (FFT)

was applied to data in each epoch using Welch's method, with a Hanning taper, 50% overlap, and a 0.25 Hz resolution. The power spectral density (μV^2/Hz) was averaged over epochs and log-transformed. Average power from the alpha (8-12 Hz) band was extracted.

Frontal alpha asymmetry scores were based on the left and right frontal electrodes F3 and F4, and calculated as: (alpha power F4 – alpha power F3)/(alpha power F4 + alpha power F3) following[49,50]. Because the alpha asymmetry values did not significantly differ between the eyes-open and eyes-closed conditions ($t(71)=1.02$, $p=.310$), data were collapsed across conditions.

PROCEDURE

The study took place at several military bases in the Netherlands. Individuals were screened by phone, and invited for study participation when meeting the eligibility criteria. At the start of the baseline assessment, participants provided written informed consent and were randomly allocated to real or sham tDCS (1:1) based on a computer-randomized list of 40 stimulator-activating codes. The study was carried out in a double-blind fashion, i.e., code-to-condition correspondence was blind to participants and experimenters during the study. Participant blinding success was not formally tested. Previous evidence suggests that individuals who are novel to tDCS cannot accurately determine whether they received sham or real tDCS[51] (but see:[52,53]). Participants and experimenters were deblinded for tDCS condition after data collection was completed. The a priori computed sample size of this trial was based on the primary hypothesis regarding emotion regulation (anticipated effect size of $d=0.73$, see **chapter 5**). With the final sample size of this trial, the present study achieved statistical power of β=0.94 to detect large effects ($d=0.8$), β=0.59 to detect medium effects (d=0.5), and β=0.15 to detect small effects ($d=0.2$) in two-sided tests with a 0.05 significance level.

Figure 1 depicts an overview of the study visits. Within six days before the first and after the last tDCS-training session, the baseline and post-assessment were carried out that included the emotional Go/No-go task and EEG recordings. The ACS was included in a set of questionnaires that was completed afterwards online. All sessions took place during participants' working hours between 6am and 9pm (depending on working shift).

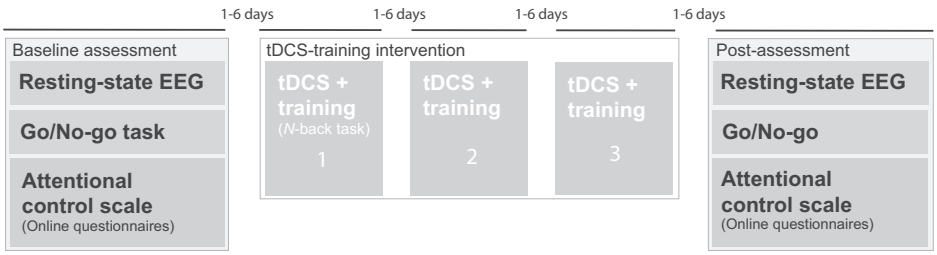


Figure 1. Overview of the tDCS-training intervention and outcome assessments of the present study. The combined tDCS-training sessions are shortly discussed in the Introduction, and in more detail reported elsewhere (see **Chapter 5**).

STATISTICAL ANALYSIS

Effects of real versus sham tDCS were analyzed in generalized linear mixed models (GLMM) based on a Gamma distribution using the "lme4" package[54] in R. Within-subject outliers in the dependent variables were excluded from analysis (>2.5 standard deviations from the mean. On average, 1.5% of Go/No-go trials in task performance data and 1.7% of Go/No-go epochs in EEG data was excluded per participant. All outcome variables were analyzed as a function of the fixed factors *Time* (baseline, post-assessment) and *Group* (real tDCS, sham tDCS), and a random intercept for *Participant*. For emotional Go/No-go task performance and the ERP analyses, an additional fixed effect for *Emotion* was added (Go-instruction: Angry=Go vs. Neutral=Go). For the ACS scores, an additional fixed effect for *Subscale* was added (Focusing vs. Shifting). To control for the influence of age, all models were repeated with *Age* as an additional fixed factor. Considering the four different outcome domains, effects with a Bonferroni-corrected $p<.0125$ (two-tailed) were considered statistically significant. Interaction effects were followed-up by post-hoc comparisons of the estimated marginal means using the "emmeans" package in R[55].

RESULTS

TDCS was well tolerated by the participants and no significant differences in tDCS-related side-effects or fluctuations in emotional state during tDCS were observed between the real tDCS group and sham tDCS group (p's>.145). A full overview of the tDCS side effects is reported in **Chapter 5**.

EMOTIONAL GO/NO-GO TASK

Task performance

No significant *Group*×*Time* interaction effects were observed (p's>.25), see **Figure 2**. **Table S1** reports the full outcomes of this analysis.

Other significant effects were found for the main effects of *Time* and *Emotion* (p's<.004), indicating performance improvements (faster RT and higher *d'*) from baseline to post-assessment and from the Neutral=Go condition to the Angry=Go condition. No other main or interaction effects were statistically significant.

In summary, these results demonstrate significant practice effects and successful manipulation of task performance by emotional condition, but show no significant effect of the tDCS-training intervention.

ERPs

Six participants were excluded from ERP analyses due to failing EEG equipment (n=3) or excessive eye blink artefacts (n=3). In the final sample of n=68 (39/29 real/sham tDCS), no significant *Group*×*Time* interaction effects were observed (p's>.26), see **Figure 2**. **Table S2** reports the full outcomes of this analysis.

Other significant effects were found for the main effect of *Time* on the N2 amplitude (*b*(SE)= -0.50(0.15), *p*=.001), showing that the N2 amplitude significantly increased from baseline to post-assessment (*p*<.001). In addition, significant interactions between *Group×Emotion* and *Group×Go/No-go×Emotion* (*Group×Emotion*: *b*(SE)= 0.42(0.19), *p*=.029; *Group×Go/No-go×Emotion*: *b*(SE)= -0.67(0.28), *p*=.016) indicated that the No-go N2 amplitude was reduced for angry versus neutral faces, but only in the sham group (contrast for No-go-N2: *p*=.029, Go-N2: *p*=.337), not in the real tDCS group (contrast for No-go-N2: *p*=.767, Go-N2: *p*=.070). In addition, the P3 latency showed a significant main effect of *Go/No-go* (*b*(SE)= -47.45(14.40), *p*=.001) and a significant *Go/No-go×Emotion* interaction (*b*(SE)= 39.54(19.50), *p*=.043), showing that the Go-P3 onset was delayed compared to the No-go P3 onset. This contrast was only significant for neutral face stimuli (*p*<.001), not for angry face stimuli (*p*=0.312). No other main or interaction effects were statistically significant.

In summary, these results show successful manipulation of the ERPs by emotion and Go/No-go condition, but no significant effects of the tDCS-training intervention.

RESTING-STATE EEG FRONTAL ALPHA ASYMMETRY

For frontal alpha asymmetry, no significant *GroupxTime* interaction effects were observed (before controlling for *Age*: *GroupxTime p*=.036; after controlling for *Age*, *p*'s>.16), see **Figure 3**. **Table S3** reports the full outcomes of this analysis. No other significant effects were observed. Together these results show no significant effects of the tDCS-training intervention on the resting-state EEG readouts.

ATTENTIONAL CONTROL SCALE

No significant *Group×Time* interaction effects or other effects were observed (*p*'s>.46), indicating no significant effects of the tDCS-training intervention on the ACS scores, see **Figure 3**. **Table S4** reports the full outcomes of this analysis.

All results reported above are based on analyses without the effect of *Age*. Unless otherwise reported, adding *Age* did not significantly change the results.

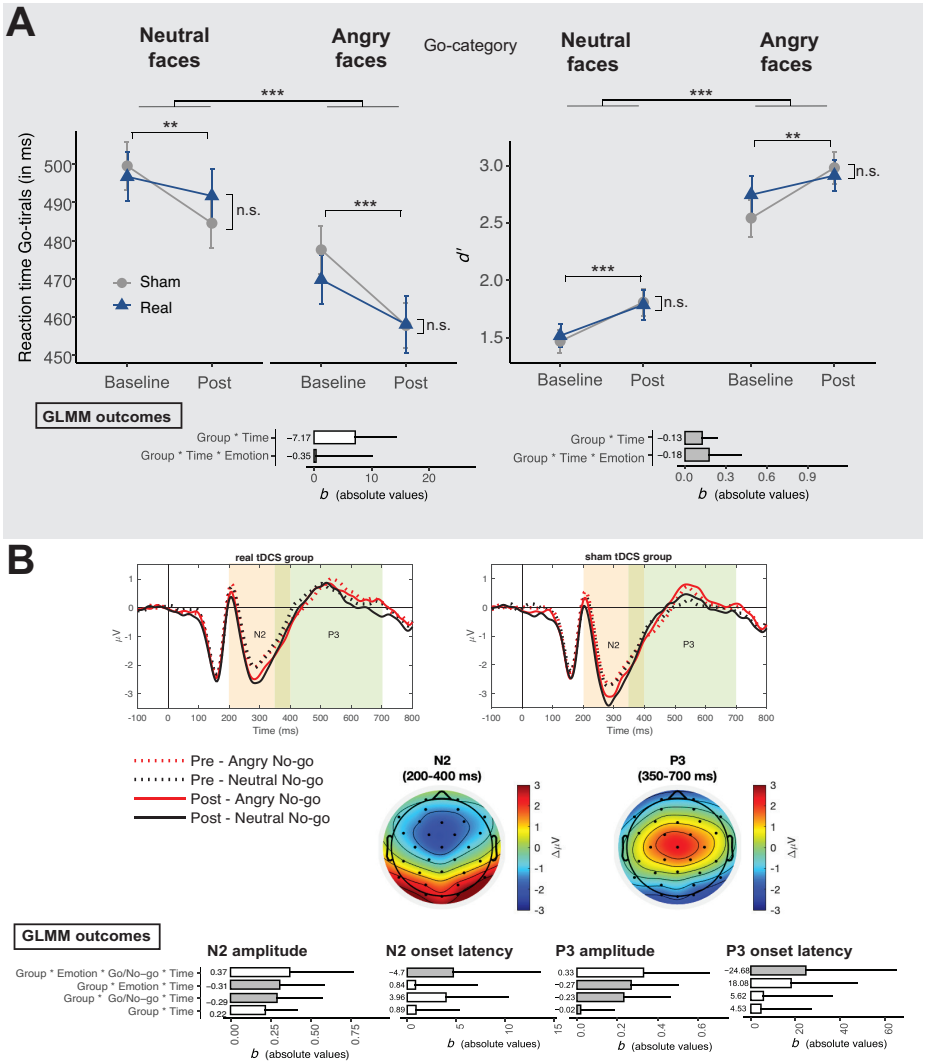


Figure 2. A) Mean values and standard error of emotional Go/No-go task performance in reaction time (RT) and sensitivity (*d'*) per group and timepoint. Error bars represent the standard error. **B)** Go/No-go task ERPs per group and the distribution of the N2 and P3 ERPs over the scalp electrodes. Stimulus onset at time = 0 ms. Plotted ERPs are the average over channels Fz, Cz, FC1, FC2, CP1, CP2. Plotted distributions reflect the change in voltage relative to ERP onset. The GLMM-estimated effects of interest are depicted with standard error. Bars represent the absolute size of the estimated effect (*b*), with grey-colored bars for negative values.

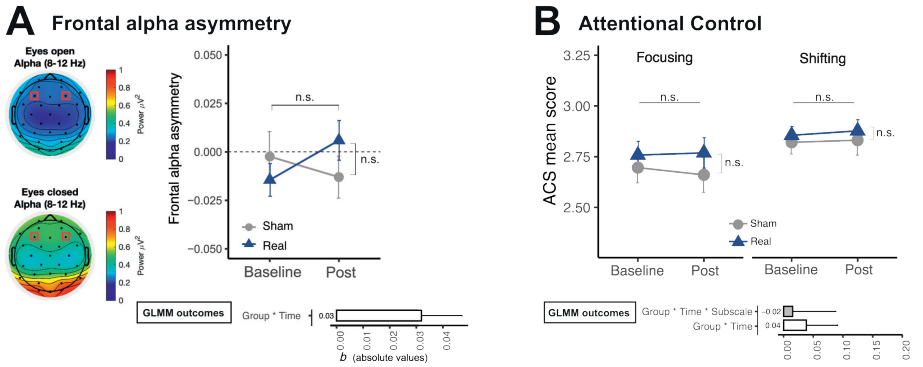


Figure 3. A) Topoplots represent average resting-state alpha power distributions for the eyes open and eyes closed condition. Frontal alpha asymmetry was based on the ratio between resting-state alpha power in the channels F3 and F4, marked in red. The graph represents the mean values of the frontal alpha asymmetry values with standard error per group and timepoint (across eyes open and eyes closed condition). **B)** Mean ACS subscale scores with standard error per group and timepoint. n.s. = not significant. The GLMM-estimated effects of interest with standard error. Bars represent the absolute size of the estimated effect (*b*), with grey-colored bars for negative values.

DISCUSSION

The present study tested effects of three sessions of anodal tDCS over the right DLPFC at 2 mA combined with emotional *N*-Back training in healthy military personnel. Results did not support the hypothesis that the real versus sham tDCS-training intervention improved Go/No-go task performance or changed associated ERPs, increased attentional control self-report scores or attenuated resting-state EEG frontal alpha asymmetry. Below we discuss four potential reasons for our null findings to consider in future tDCS research of cognitive control. These include the scope of outcome assessments, generalization and duration of tDCS-effects, the tDCS-target region and trait- and state-dependency of tDCS outcomes.

First, the outcome measures of the present study may not have been sensitive to the effects of the tDCS-training intervention. For example, on one hand, previous tDCS-cognitive training interventions have shown significant effects of tDCS already within one or several days after the intervention[25,56–59], also on the level of resting-state EEG frontal alpha asymmetry[82]. On the other hand, the resting-state frontal symmetry may reflect relatively stable trait-like mechanisms[34]. In contrast to *trait* frontal alpha asymmetry (recorded by resting-state), *state* frontal alpha asymmetry (recorded while an emotional state is induced) might be more sensitive to changes in cognitive control of emotional processes[60]. Also, resting-state EEG band power was not found to be sensitive to tDCS, at least not based on single-session tDCS studies[32]. These findings suggest that resting-state frontal alpha asymmetry might have limited sensitivity to the effects of this tDCS-training intervention. Furthermore, according to the activity-selectivity hypothesis[61], effects of tDCS selectively influence neural activity that is ongoing during stimulation, suggesting that the effects of tDCS during cognitive training may remain task- or domain-specific. If so, Go/No-go task measures in the domain

of inhibitory control may also not have been sensitive to the effects of tDCS during working memory training. This would be in line with the results of two previous studies where tDCS was ombined with working memory training: significant transfer effects of the tDCS-training intervention were found on attentional or working memory task performance, but not on Go/No-go task performance[26,62]. Taken together, the lack of significant effects in the present study may partly be explained by the limited sensitivity of the outcome measures to short-lasting, domain-specific effects of the tDCS-training intervention.

Second, the occurrence of generalized, longer-lasting effects of tDCS may depend on critical factors that were lacking in the present study. Although tDCS in this study showed very limited effects on training performance and only accelerated early-stage learning in a trait-dependent fashion (see **Chapter 5**), prior findings suggest that tDCS-cognitive training interventions may have longer-lasting effects on non-trained cognitive processes even in the absence of consistent tDCS-effects on training performance. For example, in several studies of tDCS combined with working memory or decision-making training[27,58,63], tDCS showed little or no effects during cognitive training sessions, but did show significant effects on post-intervention trained and non-trained task performance. However, while potential ceiling effects during cognitive training may be involved in the lack of tDCS-effects during training, it remains incompletely understood how tDCS could induce longer-term effects in the absence of short-term effects. It is not unlikely that the lack of tDCS-effects on the non-trained cognitive outcomes in this study reflect that tDCS-effects only generalize to non-trained cognitive processes when the trained cognitive process is effectively modulated. Furthermore, inter-session interval may play a role in the neuroplastic changes that underlie the longer-lasting and transfer effects of tDCS. In the present study, up to six days were allowed between sessions. As a result, almost half of the tDCS-training sessions were separated by more than one day. While some previous studies also allowed more than one day between sessions and still showed significant longer-lasting effects of tDCS-training interventions[23,26,59,64], there is evidence suggesting that the neuroplastic effects of (stand-alone) multisession tDCS interventions require no more than 24 hours between sessions[65–67]. Hence, generalization of effects and longer-lasting effects of tDCS may require both significant tDCS-effects on the trained function and shorter intervals between tDCS-training sessions.

Third, regarding the stimulation site, results are mixed with respect to the most effective PFC target region to modulate cognitive control. For instance, whereas the right DLPFC has been shown to be an effective target region to modulate inhibitory control during Go/No-go task performance in a number of multisession tDCS-training interventions[25,63,68], a meta-analysis of single-session tDCS-effects on inhibitory control only supported the effectivity of tDCS over the right inferior frontal gyrus and not of tDCS over the right DLPFC[18]. On the other hand, a recent multisession tDCS-cognitive training intervention targeting the right inferior frontal gyrus also showed no significant effects on inhibitory control[69,70]. These seemingly contradictory results are illustrative for mixed findings regarding electrode placement and other tDCS parameters to effectively influence cognitive processes[21]. Alternative target regions beyond the PFC possibly provide a more effective entrance for modulation of the cognitive control network with tDCS. For instance, the posterior lobes of the cerebellum are strongly connected to the PFC and have

been implicated in learning as well as cognitive control processes[71]. Initial evidence supports that tDCS over the cerebellum could have beneficial effects on cognitive control functions like attention and working memory[71].

Fourth, inter-individual variability in tDCS-response may have obscured tDCS-effects on the group-level. Individual differences were only accounted for in the present analyses by including age as a potential moderator, according to previous findings of age-dependent tDCS-effects[72-74]. Still, many other state and trait factors have been suggested to influence tDCS-response[75–77]. To gain further insight in the state-dependency of tDCS-effects, future studies are needed to systematically vary certain physiological or psychological states that appear to have a significant impact on tDCS outcomes, such as reward motivation[78], physiological arousal[79] and caffeine consumption[75,80].

LIMITATIONS

Several factors in our study may limit the generalizability of the present findings. First of all, our results are based on a sample of military personnel, in contrast to the student samples typically used in tDCS research. Military servicemembers form a population that may particularly benefit from cognitive control interventions considering the high cognitive and emotional demands of military operational contexts. On the other hand, military personnel may therefore already have relatively high cognitive control capacities, possibly leading to ceiling effects on the cognitive control-related outcome measures of the present study. The comparability and generalization of our results to other research findings and populations may therefore be limited. Moreover, the present study achieved sufficient statistical power to detect medium-to-large effect sizes (d=0.7 or higher). While such effects were hypothesized in this combination of multisession tDCS and cognitive training, estimated effect sizes of single-session tDCS in the domain of executive functions are typically in the small-to-medium range[17,81]. Our sample size may thus have been insufficient to detect group-level effects on the assessed outcome measures.

Taken together, evidence in favor of the effectivity of combined tDCS-training to enhance cognitive control processes is complemented by studies showing null results. Our results conform with the latter and thereby contribute to the mixed literature of cognitive benefits of multisession tDCS over the PFC. This may indicate that the standard range of parameters in tDCS-cognitive training may not be effective to induce significant neuroplastic changes in cognitive control networks, at least not in populations like military servicemembers.

CONCLUSION

In conclusion, the present study found no evidence for changes in inhibitory and attentional control or their neural correlates in EEG activity after three sessions of anodal tDCS over the right DLPFC combined with emotional *N*-Back training in military personnel. These results indicate that the durability and generalizability of effects on cognitive control of tDCS-training interventions, with parameters as applied here, may be limited.

REFERENCES

1. Martin K, McLeod E, Périard J, Rattray B, Keegan R, Pyne DB. The Impact of Environmental Stress on Cognitive Performance: A Systematic Review. *Human Factors: The Journal of the Human Factors and Ergonomics Society*. 2019;61(8):1205-1246. doi:10.1177/0018720819839817

2. Kavanagh J. Stress and Performance A Review of the Literature and Its Applicability to the Military. Published online 2005. Accessed August 31, 2021. http://www.rand.org/

3. Sareen J, Cox BJ, Afifi TO, et al. Combat and peacekeeping operations in relation to prevalence of mental disorders and perceived need for mental health care: findings from a large representative sample of military personnel. *Arch Gen Psychiatry*. 2007;64(7):843-852. doi:10.1001/archpsyc.64.7.843

4. van der Wal SJ, Vermetten E, Elbert G. Long-term development of post-traumatic stress symptoms and associated risk factors in military service members deployed to Afghanistan: Results from the PRISMO 10-year follow-up. *European Psychiatry*. 2021;64(1):e10. doi:10.1192/j.eurpsy.2020.113

5. van der Wal SJ, Geuze E, Vermetten E. Long-term risk for mental health symptoms in Dutch ISAF veterans: the role of perceived social support. *Psychological Medicine*. Published online January 18, 2022:1-11. doi:10.1017/S0033291721005389

6. Kalisch R, Müller MB, Tüscher O. A conceptual framework for the neurobiological study of resilience. *Behavioral and Brain Sciences*. 2015;38:e92. doi:10.1017/S0140525X1400082X

7. Gratton G, Cooper P, Fabiani M, Carter CS, Karayanidis F. Dynamics of cognitive control: Theoretical bases, paradigms, and a view for the future. *Psychophysiology*. 2018;55(3). doi:10.1111/PSYP.13016

8. Ben-Avraham R, Afek A, Berezin Cohen N, et al. Feasibility and preliminary effectiveness of mobile cognitive control training during basic combat training in the military. *Military Psychology*. Published online 2021. doi:10.1080/08995605.2021.1969162/SUPPL_FILE/HMLP_A_1969162_SM1240.ZIP

9. Jha AP, Stanley EA, Kiyonaga A, Wong L, Gelfand L. Examining the Protective Effects of Mindfulness Training on Working Memory Capacity and Affective Experience. *Emotion*. 2010;10(1):54-64. doi:10.1037/A0018438

10. Buchanan JJ, Bedard RR, Kelly KR, et al. The Benefit of Mental Skills Training on Performance and Stress Response in Military Personnel. Published online 2020. doi:10.3389/fpsyg.2019.02964

11. Niendam TA, Laird AR, Ray KL, Dean YM, Glahn DC, Carter CS. Meta-analytic evidence for a superordinate cognitive control network subserving diverse executive functions. *Cognitive, Affective and Behavioral Neuroscience*. 2012;12(2):241-268. doi:10.3758/s13415-011-0083-5

12. Kohn N, Eickhoff SB, Scheller M, Laird AR, Fox PT, Habel U. Neural network of cognitive emotion regulation — An ALE meta-analysis and MACM analysis. *Neuroimage*. 2014;87:345-355. doi:10.1016/j.neuroimage.2013.11.001

13. Plewnia C, Schroeder PA, Wolkenstein L. Targeting the biased brain: Non-invasive brain stimulation to ameliorate cognitive control. *The Lancet Psychiatry*. 2015;2(4):351-356. doi:10.1016/S2215-0366(15)00056-5

14. Stagg CJ, Antal A, Nitsche MA. Physiology of Transcranial Direct Current Stimulation. *Journal of ECT*. 2018;34(3):144-152. doi:10.1097/YCT.0000000000000510

15. Knotkova H, Nitsche MA, Bikson M, Woods AJ, eds. *Practical Guide to Transcranial Direct Current Stimulation*. Springer International Publishing; 2019. doi:10.1007/978-3-319-95948-1

16. Mendes AJ, Pacheco-Barrios K, Lema A, et al. Modulation of the cognitive event-related potential P3 by transcranial direct current stimulation: Systematic review and meta-analysis. *Neuroscience & Biobehavioral Reviews*. Published online November 3, 2021. doi:10.1016/J.NEUBIOREV.2021.11.002

17. Wischnewski M, Mantell KE, Opitz A. Identifying regions in prefrontal cortex related to working memory improvement: A novel meta-analytic method using electric field modeling. *Neuroscience & Biobehavioral Reviews*. 2021;130:147-161. doi:10.1016/J.NEUBIOREV.2021.08.017

18. Schroeder PA, Schwippel T, Wolz I, Svaldi J. Meta-analysis of the effects of transcranial direct current stimulation on inhibitory control. *Brain Stimulation*. Published online 2020. doi:10.1016/j.brs.2020.05.006

19. Dedoncker J, Brunoni AR, Baeken C, Vanderhasselt MA. A Systematic Review and Meta-Analysis of the Effects of Transcranial Direct Current Stimulation (tDCS) Over the Dorsolateral Prefrontal Cortex in Healthy and Neuropsychiatric Samples: Influence of Stimulation Parameters. *Brain Stimulation*. 2016;9(4):501-517. doi:10.1016/j.brs.2016.04.006

20. Nitsche MA, Paulus W. Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. *Neurology*. 2001;57(10):1899-1901. doi:10.1212/WNL.57.10.1899

21. Farhat LC, Carvalho AF, Solmi M, Brunoni AR. Evidence-based umbrella review of cognitive effects of prefrontal tDCS. *Social Cognitive and Affective Neuroscience*. 2020;2020:1-18. doi:10.1093/SCAN/NSAA084

22. Berryhill ME, Martin D. Cognitive Effects of Transcranial Direct Current Stimulation in Healthy and Clinical Populations: An Overview. *Journal of ECT*. 2018;34(3):e25-e35. doi:10.1097/YCT.0000000000000534

23. Looi CY, Duta M, Brem AK, Huber S, Nuerk HC, Cohen Kadosh R. Combining brain stimulation and video game to promote long-term transfer of learning and cognitive enhancement. *Scientific Reports*. Published online 2016. doi:10.1038/srep22003

24. Jones KT, Peterson DJ, Blacker KJ, Berryhill ME. Frontoparietal neurostimulation modulates working memory training benefits and oscillatory synchronization. *Brain Research*. 2017;1667:28-40. doi:10.1016/j.brainres.2017.05.005

25. Dousset C, Ingels A, Schröder E, et al. Transcranial Direct Current Stimulation Combined With Cognitive Training Induces Response Inhibition Facilitation Through Distinct Neural Responses According to the Stimulation Site: A Follow-up Event-Related Potentials Study. *Clinical EEG and Neuroscience*. 2021;52(3):181-192. doi:10.1177/1550059420958967

26. Au J, Katz B, Buschkuehl M, et al. Enhancing Working Memory Training with Transcranial Direct Current Stimulation. *Journal of Cognitive Neuroscience*. 2016;28(9):1419-1432. doi:10.1162/jocn_a_00979

27. Talsma LJ, Kroese HA, Slagter HA. Boosting Cognition: Effects of Multiple-Session Transcranial Direct Current Stimulation on Working Memory. *Journal of Cognitive Neuroscience*. 2017;29(4):755-768. doi:10.1162/jocn_a_01077

28. Jaeggi SM, Buschkuehl M, Perrig WJ, Meier B. The concurrent validity of the N-back task as a working memory measure. *http://dx.doi.org/101080/09658211003702171*. 2010;18(4):394-412. doi:10.1080/09658211003702171

29. Schweizer S, Grahn J, Hampshire A, Mobbs D, Dalgleish T. Training the Emotional Brain: Improving Affective Control through Emotional Working Memory Training. *Journal of Neuroscience*. 2013;33(12):5301-5311. doi:10.1523/JNEUROSCI.2593-12.2013

30. Huster RJ, Messel MS, Thunberg C, Raud L. The P300 as marker of inhibitory control – Fact or fiction? *Cortex*. 2020;132:334-348. doi:10.1016/J.CORTEX.2020.05.021

31. Nieuwenhuis S, Yeung N, van den Wildenberg W, Ridderinkhof KR. Electrophysiological correlates of anterior cingulate function in a go/no-go task: Effects of response conflict and trial type frequency. *Cognitive, Affective, & Behavioral Neuroscience 2003 3:1*. 2003;3(1):17-26. doi:10.3758/CABN.3.1.17

32. Chan MMY, Yau SSY, Han YMY. The neurobiology of prefrontal transcranial direct current stimulation (tDCS) in promoting brain plasticity: A systematic review and meta-analyses of human and rodent studies. *Neuroscience & Biobehavioral Reviews*. 2021;125:392-416. doi:10.1016/J.NEUBIOREV.2021.02.035

33. Tu Y, Cao J, Guler S, et al. Perturbing fMRI brain dynamics using transcranial direct current stimulation. *Neuroimage*. 2021;237:118100. doi:10.1016/j.neuroimage.2021.118100

34. Harmon-Jones E, Gable PA. On the role of asymmetric frontal cortical activity in approach and withdrawal motivation: An updated review of the evidence. *Psychophysiology*. 2018;55(1):e12879. doi:10.1111/psyp.12879

35. Allen JJB, Coan JA, Nazarian M. Issues and assumptions on the road from raw signals to metrics of frontal EEG asymmetry in emotion. *Biological Psychology*. 2004;67(1-2):183-218. doi:10.1016/J.BIOPSYCHO.2004.03.007

36. Smith EE, Reznik SJ, Stewart JL, Allen JJB. Assessing and conceptualizing frontal EEG asymmetry: An updated primer on recording, processing, analyzing, and interpreting frontal alpha asymmetry. *International Journal of Psychophysiology*. 2017;111:98-114. doi:10.1016/J.IJPSYCHO.2016.11.005

37. Gable PA, Neal LB, Threadgill AH. Regulatory behavior and frontal activity: Considering the role of revised-BIS in relative right frontal asymmetry. *Psychophysiology*. 2018;55(1):e12910. doi:10.1111/PSYP.12910

38. Schutter DJLG, Harmon-Jones E. The corpus callosum: A commissural road to anger and aggression. *Neuroscience and Biobehavioral Reviews*. Published online 2013. doi:10.1016/j.neubiorev.2013.07.013

39. Aron AR, Robbins TW, Poldrack RA. Inhibition and the right inferior frontal cortex: One decade on. *Trends in Cognitive Sciences*. 2014;18(4):177-185. doi:10.1016/j.tics.2013.12.003

40. Delorme A, Makeig S. *EEGLAB: An Open Source Toolbox for Analysis of Single-Trial EEG Dynamics Including Independent Component Analysis*. Vol 134.; 2004.

41. Lopez-Calderon J, Luck SJ. ERPLAB: an open-source toolbox for the analysis of event-related potentials. *Frontiers in Human Neuroscience*. 2014;8(1 APR):213. doi:10.3389/fnhum.2014.00213

42. Schulz KP, Fan J, Magidina O, Marks DJ, Hahn B, Halperin JM. Does the emotional go/no-go task really measure behavioral inhibition?. Convergence with measures on a non-emotional analog. *Archives of Clinical Neuropsychology*. Published online 2007. doi:10.1016/j.acn.2006.12.001

43. Gladwin TE, Möbius M, Vink M. Threat-induced impulsivity in Go/Nogo tasks: Relationships to task-relevance of emotional stimuli and virtual proximity. *Consciousness and Cognition*. 2019;74:102795. doi:10.1016/j.concog.2019.102795

44. Ma DS, Correll J, Wittenbrink B. The Chicago face database: A free stimulus set of faces and norming data. *Behavior Research Methods*. 2015;47(4):1122-1135. doi:10.3758/S13428-014-0532-5/FIGURES/2

45. Stanislaw, H., & Todorov, N. (1999). Calculation of signal detection theory measures. Behavior research methods, instruments, & computers, 31(1), 137-149.

46. Kiesel A, Miller J, Jolicoeur P, et al. Measurement of ERP latency differences: A comparison of single-participant and jackknife-based scoring methods. *Psychophysiology*. 2008;45(2):250-274. doi:10.1111/J.1469-8986.2007.00618.X

47. Derryberry D, Reed MA. Anxiety-related attentional biases and their regulation by attentional control. *Journal of Abnormal Psychology*. Published online 2002. doi:10.1037/0021-843X.111.2.225

48. Judah MR, Grant DM, Mills AC, Lechner W V. Factor structure and validation of the attentional control scale. *Cogn Emot*. 2014;28(3):433-451. doi:10.1080/02699931.2013.835254

49. Hofman D, Schutter DJLG. Asymmetrical frontal resting-state beta oscillations predict trait aggressive tendencies and behavioral inhibition. *Social Cognitive and Affective Neuroscience*. 2012;7(7):850-857. doi:10.1093/SCAN/NSR060

50. Schutter DJLG, de Weijer AD, Meuwese JDI, Morgan B, van Honk J. Interrelations between motivational stance, cortical excitability, and the frontal electroencephalogram asymmetry of emotion: A transcranial magnetic stimulation study. *Human Brain Mapping*. 2008;29(5):574-580. doi:10.1002/hbm.20417

51. Ambrus GG, Al-Moyed H, Chaieb L, Sarp L, Antal A, Paulus W. The fade-in – Short stimulation – Fade out approach to sham tDCS – Reliable at 1 mA for naïve and experienced subjects, but not investigators. *Brain Stimulation*. 2012;5(4):499-504. doi:10.1016/j.brs.2011.12.001

52. Turi Z, Csifcsák G, Boayue NM, et al. Blinding is compromised for transcranial direct current stimulation at 1 mA for 20 min in young healthy adults. *European Journal of Neuroscience*. 2019;50(8):3261-3268. doi:10.1111/EJN.14403

53. Greinacher R, Buhôt L, Möller L, Learmonth G. The time course of ineffective sham-blinding during low-intensity (1 mA) transcranial direct current stimulation. *European Journal of Neuroscience*. 2019;50(8):3380-3388. doi:10.1111/ejn.14497

54. Bates D, Mächler M, Bolker B, Walker S. Fitting Linear Mixed-Effects Models Using lme4. *Journal of Statistical Software*. 2015;67(1). doi:10.18637/jss.v067.i01

55. Lenth R V. emmeans: Estimated Marginal Means, aka Least-Squares Means. R package version 1.7.0. Published online 2021.

56. Katz B, Au J, Buschkuehl M, et al. Individual differences and long-term consequences of tDCS-augmented cognitive training. *Journal of Cognitive Neuroscience*. Published online 2017. doi:10.1162/jocn_a_01115

57. Martin DM, Liu R, Alonzo A, et al. Can transcranial direct current stimulation enhance outcomes from cognitive training? A randomized controlled trial in healthy participants. *The International Journal of Neuropsychopharmacology*. 2013;16(09):1927-1936. doi:10.1017/S1461145713000539

58. Ruf SP, Fallgatter AJ, Plewnia C. Augmentation of working memory training by transcranial direct current stimulation (tDCS). *Scientific Reports*. 2017;7(1):876. doi:10.1038/s41598-017-01055-1

59. Weller S, Nitsche MA, Plewnia C. Enhancing cognitive control training with transcranial direct current stimulation: a systematic parameter study. *Brain Stimulation*. 2020;13(5):1358-1369. doi:10.1016/J.BRS.2020.07.006

60. Goodman RN, Rietschel JC, Lo LC, Costanzo ME, Hatfield BD. Stress, emotion regulation and cognitive performance: The predictive contributions of trait and state relative frontal EEG alpha asymmetry. *International Journal of Psychophysiology*. 2013;87(2):115-123. doi:10.1016/J.IJPSYCHO.2012.09.008

61. Bikson M, Rahman A. Origins of specificity during tDCS: anatomical, activity-selective, and input-bias mechanisms. *Frontiers in Human Neuroscience*. 2013;0(OCT):688. doi:10.3389/FNHUM.2013.00688

62. Filmer HL, Lyons M, Mattingley JB, Dux PE. Anodal tDCS applied during multitasking training leads to transferable performance gains. *Scientific Reports 2017 7:1*. 2017;7(1):1-11. doi:10.1038/s41598-017-13075-y

63. Gilmore CS, Dickmann PJ, Nelson BG, Lamberty GJ, Lim KO. Transcranial Direct Current Stimulation (tDCS) paired with a decision-making task reduces risk-taking in a clinically impulsive sample. *Brain Stimulation*. 2018;11(2):302-309. doi:10.1016/J.BRS.2017.11.011

64. Lu H, Gong Y, Huang P, et al. Effect of Repeated Anodal HD-tDCS on Executive Functions: Evidence From a Pilot and Single-Blinded fNIRS Study. *Front Hum Neurosci*. 2021;14. doi:10.3389/FNHUM.2020.583730

65. Alonzo A, Brassil J, Taylor JL, Martin D, Loo CK. Daily transcranial direct current stimulation (tDCS) leads to greater increases in cortical excitability than second daily transcranial direct current stimulation. *Brain Stimulation*. 2012;5(3):208-213. doi:10.1016/J.BRS.2011.04.006

66. Boggio PS, Nunes A, Rigonatti SP, Nitsche MA, Pascual-Leone A, Fregni F. Repeated sessions of noninvasive brain DC stimulation is associated with motor function improvement in stroke patients. *Restorative Neurology and Neuroscience*. 2007;25:123-129.

67. Goldsworthy MR, Pitcher JB, Ridding MC. Spaced Noninvasive Brain Stimulation: Prospects for Inducing Long-Lasting Human Cortical Plasticity. *Neurorehabilitation and Neural Repair*. 2015;29(8):714-721. doi:10.1177/1545968314562649

68. Verveer I, Remmerswaal D, van der Veen FM, Franken IHA. Long-term tDCS effects on neurophysiological measures of cognitive control in tobacco smokers. *Biological Psychology*. 2020;156:107962. doi:10.1016/j.biopsycho.2020.107962

69. Westwood SJ, Bozhilova N, Criaud M, et al. The effect of transcranial direct current stimulation (tDCS) combined with cognitive training on EEG spectral power in adolescent boys with ADHD: A double-blind, randomized, sham-controlled trial. *IBRO Neuroscience Reports*. 2022;12:55-64. doi:10.1016/J.IBNEUR.2021.12.005

70. Westwood SJ, Criaud M, Lam SL, et al. Transcranial direct current stimulation (tDCS) combined with cognitive training in adolescent boys with ADHD: a double-blind, randomised, sham-controlled trial. *Psychological Medicine*. Published online 2021:1-16. doi:10.1017/S0033291721001859

71. Billeri L, Naro A. A narrative review on non-invasive stimulation of the cerebellum in neurological diseases. *Neurological Sciences*. 2021;42(6):2191-2209. doi:10.1007/S10072-021-05187-1/TABLES/1

72. Perceval G, Flöel A, Meinzer M. Can transcranial direct current stimulation counteract age-associated functional impairment? *Neuroscience & Biobehavioral Reviews*. 2016;65:157-172. doi:10.1016/J.NEUBIOREV.2016.03.028

73. Leach RC, McCurdy MP, Trumbo MC, Matzen LE, Leshikar ED. Differential Age Effects of Transcranial Direct Current Stimulation on Associative Memory. *The Journals of Gerontology: Series B*. 2019;74(7):1163-1173. doi:10.1093/GERONB/GBY003

74. Antonenko D, Nierhaus T, Meinzer M, et al. Age-dependent effects of brain stimulation on network centrality. *Neuroimage*. 2018;176:71-82. doi:10.1016/J.NEUROIMAGE.2018.04.038

75. Zulkifly MFM, Merkohitaj O, Brockmöller J, Paulus W. Confounding effects of caffeine on neuroplasticity induced by transcranial alternating current stimulation and paired associative stimulation. *Clinical Neurophysiology*. 2021;132(6):1367-1379. doi:10.1016/J.CLINPH.2021.01.024

76. Stephens JA, Jones KT, Berryhill ME. Task demands, tDCS intensity, and the COMT val-158met polymorphism impact tDCS-linked working memory training gains. *Scientific Reports 2017 7:1*. 2017;7(1):1-11. doi:10.1038/s41598-017-14030-7

77. Krause B, Kadosh RC. Not all brains are created equal: the relevance of individual differences in responsiveness to transcranial electrical stimulation. *Frontiers in Systems Neuroscience*. 2014;8(FEB). doi:10.3389/FNSYS.2014.00025

78. Jones KT, Gözenman F, Berryhill ME. The strategy and motivational influences on the beneficial effect of neurostimulation: A tDCS and fNIRS study. *Neuroimage*. 2015;105:238-247. doi:10.1016/J.NEUROIMAGE.2014.11.012

79. Esposito M, Ferrari C, Fracassi C, Miniussi C, Brignani D. Responsiveness to left-prefrontal tDCS varies according to arousal levels. *European Journal of Neuroscience*. 2022;55(3):762-777. doi:10.1111/EJN.15584

80. Zulkifly MFM, Merkohitaj O, Paulus W. Transcranial alternating current stimulation induced excitatory aftereffects are abolished by decaffeinated espresso and reversed into inhibition by espresso with caffeine. *Clinical Neurophysiology*. 2020;131(3):778-779. doi:10.1016/J.CLINPH.2019.11.062

81. Brunoni AR, Vanderhasselt MA. Working memory improvement with non-invasive brain stimulation of the dorsolateral prefrontal cortex: A systematic review and meta-analysis. *Brain and Cognition*. 2014;86:1-9. doi:10.1016/j.bandc.2014.01.008

82. Forcano L, Castellano M, Cuenca-Royo A, et al. Prefrontal Cortex Neuromodulation Enhances Frontal Asymmetry and Reduces Caloric Intake in Patients with Morbid Obesity. Obesity. 2020;28(4):696-705. doi:10.1002/OBY.22745

APPENDIX

Table S1. Outcomes of full GLMM analyzing Go/No-go task performance.

		RT			d'		
			Variance	***SD***		***Variance***	***SD***
Random effects	Variance of random intercept for Participant		582.40	24.13		0.19	0.43
	Residual		2.71E-03	5.20E-02		0.08	0.28
		b	**SE**	***p***	***b***	**SE**	***p***
Fixed effects	*(Intercept)*	*501.40*	*8.99*	*<.001*	*1.62*	*0.14*	*<.001*
	Group	-1.82	12.29	.882	0.09	0.18	.616
	Emotion	-21.78	5.05	<.001	1.03	0.11	<.001
	Time	-14.71	5.09	.004	0.28	0.08	<.001
	Group * Emotion	-5.64	6.90	.413	0.09	0.15	.545
	Group * Time	7.17	7.06	.310	-0.13	0.11	.253
	Emotion * Time	-4.82	7.03	.493	0.17	0.17	.304
	Group * Emotion * Time	-0.35	9.70	.971	-0.18	0.23	.445

Table S2. Outcomes of full GLMM analyzing Go/No-go task ERPs.

		Amplitude			Latency		
N2		***Variance***		***SD***	***Variance***		***SD***
Random effects	Variance of random intercept for Participant		0.45	0.67		157.05	12.53
	Residual		4.7E-05	6.9E-03		1.7E-03	4.1E-02
		b	**SE**	***p***	***b***	**SE**	***p***
Fixed effects	*(Intercept)*	*97.86*	*0.34*	*<.001*	*359.86*	*5.98*	*<.001*
	Group	0.39	0.45	.377	-6.57	7.96	.409
	Emotion	-0.14	0.15	.353	-0.15	3.38	.963
	Go/No-go	-0.16	0.15	.273	0.88	3.41	.796
	Time	-0.50	0.15	.001	-1.67	3.41	.625
	Group * Emotion	0.42	0.19	.029	-3.94	4.40	.370
	Group * Go/No-go	0.38	0.20	.053	-2.68	4.44	.546
	Emotion * Go/No-go	0.33	0.21	.109	1.18	4.80	.806
	Group * Time	0.22	0.20	.267	0.89	4.43	.840
	Emotion * Time	0.07	0.21	.733	-2.25	4.81	.639
	Go/No-go * Time	-0.06	0.21	.791	-3.03	4.82	.529

■ **Table S2.** (Continued)

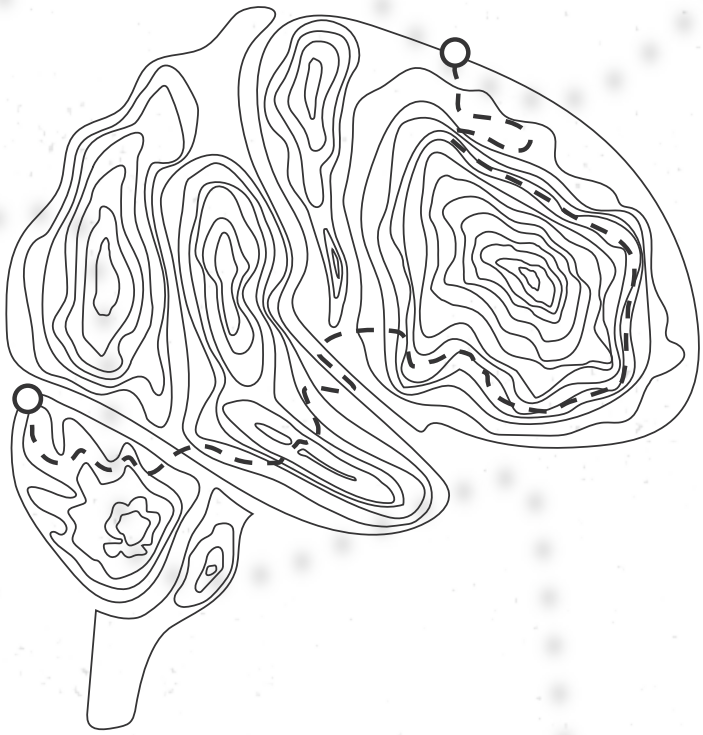
		Amplitude			Latency		
		b	**SE**	***p***	***b***	**SE**	***p***
	Group * Emotion * Go/ No-go	-0.67	0.28	.016	4.26	6.24	.495
	Group * Emotion * Time	-0.31	0.28	.267	0.84	6.24	.893
	Group * Go/No-go * Time	-0.29	0.28	.296	3.96	6.28	.528
	Emotion * Go/No-go * Time	0.01	0.30	.969	3.50	6.79	.606
	Group * Emotion * Go/ No-go * Time	0.37	0.39	.346	-4.70	8.81	.594
P3		***Variance***		***SD***	***Variance***		***SD***
Random effects	Variance of random intercept for Participant		0.24	0.49		650.04	25.50
	Residual		3.0E-05	5.5E-03		6.4E-03	8.0E-02
		b	**SE**	***p***	***b***	**SE**	***p***
Fixed effects	*(Intercept)*	*99.83*	*0.24*	*<.001*	*589.78*	*14.62*	*<.001*
	Group	0.41	0.31	.194	-16.85	20.41	.409
	Emotion	0.12	0.12	.309	-10.63	13.89	.444
	Go/No-go	0.18	0.12	.143	-47.45	14.40	.001
	Time	0.18	0.12	.142	-2.46	15.83	.876
	Group * Emotion	0.24	0.16	.139	-8.05	19.53	.680
	Group * Go/No-go	0.05	0.16	.746	20.79	19.33	.282
	Emotion * Go/No-go	-0.09	0.17	.617	39.54	19.50	.043
	Group * Time	-0.02	0.16	.910	4.53	22.35	.839
	Emotion * Time	-0.04	0.17	.832	-28.30	19.98	.157
	Go/No-go * Time	-0.10	0.17	.551	-10.62	22.08	.631
	Group * Emotion * Go/ No-go	-0.31	0.23	.184	-4.49	27.05	.868
	Group * Emotion * Time	-0.27	0.23	.242	18.08	29.65	.542
	Group * Go/No-go * Time	-0.23	0.23	.314	5.62	30.83	.855
	Emotion * Go/No-go * Time	0.08	0.25	.758	30.79	27.62	.265
	Group * Emotion * Go/ No-go * Time	0.33	0.33	.310	-24.68	40.75	.545

Table S3. Outcomes of full GLMM analyzing resting-state EEG frontal alpha asymmetry.

			Variance	*SD*
Random effects	Variance of random intercept for Participant		1.5E-03	3.9E-02
	Residual		2.5E-05	5.0E-03
		b	**SE**	***p***
Fixed effects	*(Intercept)*	*10.00*	*1.3E-02*	*<.001*
	Group	-1.2E-02	1.8E-02	.496
	Time	-1.4E-02	1.1E-02	.214
	Group * Time	3.2E-02	1.5E-02	.036

Table S4. Outcomes of full GLMM analyzing ACS subscales.

			Variance	*SD*
Random effects	Variance of random intercept for Participant		0.06	0.25
	Residual		0.01	0.10
		b	**SE**	***p***
Fixed effects	*(Intercept)*	*2.79*	*0.08*	*<.001*
	Group	0.08	0.11	.506
	Time	-0.02	0.04	.518
	Subscale	0.12	0.04	.001
	Group * Time	0.04	0.05	.464
	Group * Subscale	-0.02	0.05	.726
	Time * Subscale	0.02	0.05	.755
	Group * Time * Subscale	-0.02	0.07	.830



CHAPTER 7

| General discussion

SUMMARY

Chapter 2 described a systematic review and meta-analysis on the effects of single-session rTMS and tDCS of the prefrontal cortex on emotional stress reactivity in healthy volunteers. The overall evidence supported a significant effect of anodal tDCS on downregulating emotional reactivity, with an effect size of Hedges' g = -0.16 ($CI_{95\%}$ = [-0.33, 0.00]). This indicated that anodal tDCS of the prefrontal cortex can affect stress-related emotional processes, and thereby supported the feasibility to evaluate its effect in a clinical study. However, the effect of tDCS varied substantially between studies. The relatively low sample sizes of most studies, compared to the overall small effect size and outcome variability of tDCS-effects, indicated that well-powered tDCS studies were necessary. In addition, some single study outcomes suggested that the positive effect of tDCS on emotional reactivity was stronger when tDCS was combined with a task that activated emotion regulation processes. Following these observations, the effects of anodal tDCS of the prefrontal cortex were tested in two randomized controlled trials (RCTs).

The first RCT (**Chapter 3** and **4**) was based on the idea that inhibitory control plays a facilitating role in the recovery from symptoms of PTSD, anxiety and aggression regulation problems. Five sessions of anodal tDCS over the right inferior frontal gyrus were combined with computerized inhibitory control training. The effectivity of this intervention was tested in a large military patient sample (n=100). The RCT results were presented in **Chapter 3**. No evidence was found for the effectivity of the real versus sham tDCS-training intervention on inhibitory control performance or on stress-related symptoms. More specifically, real versus sham tDCS showed no significant immediate effect on inhibitory control training performance (stop-signal task), and no significant longer-lasting transfer effects on post-intervention inhibitory control (emotional Go/No-go task and the implicit associated test). Also on the clinical level, real versus sham tDCS showed no significant effect on PTSD, anxiety or aggression symptoms immediately following the intervention, after three months or after one year. Possible explanations for the lack of significant tDCS-effects could have been the easy and repetitive nature of the training task, which could have prevented sufficient induction of learning and associated synaptic plasticity during tDCS. In combination with a relatively low current intensity of 1.25 mA, the tDCS protocol may have been suboptimal to modulate cortical excitability in the target region. Regarding the acceptability of tDCS (**Chapter 4**), military patients and caregivers overall found tDCS a tolerable and acceptable treatment tool for stress-related disorders. The potential to combine psychotherapeutic with brain-based neurobiological treatment methods was viewed as the main positive aspect of tDCS, that is, tDCS as an add-on intervention. Anticipated hurdles in the practical implementation of tDCS were related to travelling for frequent treatment sessions, which shows the relevance of scalable techniques like tDCS that allow for home-based solutions.

In the second RCT (**Chapter 5** and **6**), the tDCS current intensity was increased to 2.0 mA and a different electrode montage was used in combination with a different and more difficult

cognitive training on a working memory task. Additionally, emotional and stress-related components were incorporated into the training task to better engage stress regulation pathways. EEG recordings were also included to allow studying effects of tDCS on the level of brain activity. The aim of this study was to investigate the potential of tDCS to increase stress-related psychological resilience. Anodal tDCS of the dorsolateral prefrontal cortex was hypothesized to enhance emotional working memory capacity and thereby facilitate top-down stress regulation. This hypothesis was tested in a large sample of healthy military personnel (n=79). Three sessions with anodal tDCS of the right dorsolateral prefrontal cortex were combined with emotional working memory training. Results showed no group-level evidence for the effectivity of the real versus sham tDCS-training intervention on the assessed outcome variables. More specifically, no significant tDCS group differences appeared in emotional working memory performance or threat-related responses (**Chapter 5**). Likewise, no significant tDCS group differences appeared in inhibitory control and attentional control, based on pre-to-post intervention task performance, self-report and electrophysiological measures (Go/No-go task event-related potentials and resting-state frontal alpha asymmetry) (**Chapter 6**). Interestingly, however, exploratory analyses in **Chapter 5** did reveal a short-lasting, trait-dependent effect of tDCS during the first tDCS-training session. That is, during the first session, real versus sham tDCS significantly enhanced emotional working memory training performance depending on individual characteristics like younger age and a higher EEG theta/beta power ratio.

The main question central to this thesis was: Can treatment and resilience for stress-related mental health symptoms in the military be improved by boosting prefrontal cortex functions using tDCS?'. Overall, no evidence was found for clinical utility in military personnel of the tDCS interventions as described in the present work. These somewhat disappointing findings motivate to critically evaluate our tDCS approach and study designs, and to consider more fruitful ways to investigate the clinical utility of non-invasive brain stimulation in the context of stress-related mental health.

CRITICAL EVALUATION

The studies presented in this thesis had several methodological strength and shortcomings, as summarized in Box 7.1, that together shape the conditions of generalizability of our results to other populations and other study set-ups. One aspect of methodological strength incorporated in the design of the two experimental studies (described in **Chapters 3** and **5**) concerns the conceptual replication of previously shown effects of anodal tDCS over the right lateral prefrontal cortex (PFC) on cognitive training performance, in larger samples. However, by showing largely non-significant effects of tDCS, our results raise questions on the effectivity of the overall tDCS approach adopted in this thesis. As the methodological considerations of each study are discussed in the respective chapters, this chapter aims to take on a bird's eye view and consider the present work from a broader perspective. The clinical potential of tDCS in the domain of stress-related cognition and emotion is evaluated by two questions. First, what are the drawbacks from our approach considering the focus on cognitive training and anodal stimulation of the PFC? Second, does the limited mechanistic understanding of tDCS at present permit conclusions on its (clinical) effectivity?

Box 7.1 Main methodological strengths and limitations

Strengths:

- *Multiple measurement levels:* Outcome measurements spanned multiple levels, including neurophysiology (e.g., startle reflex and EEG), behavior (e.g., cognitive tasks), phenomenology (e.g., self-reports on emotional state) and symptomatology.
- *Reliability of results:* Results are derived from theory-driven study designs with large sample sizes and meta-analytic and randomized controlled trial methods.
- *Clinical relevance:* Laboratory-based tDCS research was translated to a relevant population with a transdiagnostic range of stress-related symptoms and cognitive capacities.

Limitations:

- *Generalizability of results:* Potentially suboptimal tDCS parameters, such as the number and spacing of tDCS sessions, may limit the generalizability of results to other tDCS protocols.
- *Sensitivity of outcome measures:* Signs of ceiling and floor effects in some of the outcome measures, such as the cognitive training and stress regulation test, may have hindered the manifestation of tDCS-effects on these outcome measures.

DRAWBACKS OF FOCUSING ON COGNITIVE TRAINING AND THE PREFRONTAL CORTEX

There is substantial evidence supporting a relationship of adaptive stress regulation with activity in right lateral PFC regions and with higher-order cognitive functions such as working

memory[1,2]. This led to the working model central to this thesis that stress regulation could be improved by facilitating activity in this region using tDCS. In addition, following the activity-selective hypothesis[3] as discussed in the introduction (**Chapter 1**), it was assumed that tDCS effectivity would be higher and more specific to a cognitive process of interest when tDCS was combined with a cognitive training task. Below, we comment upon three major challenges of this working model with respect to cognitive training paradigms, the complex dynamics of PFC activity, and the translation from brain activity measures to brain stimulation protocols.

1. Limitations of cognitive training

TDCS was combined with cognitive training to activate and promote plasticity in the associated neural networks. Cognitive training without tDCS has been shown to beneficially influence cognitive functioning. For example, cognitive training during neurorehabilitation can help to restore some of the specific cognitive deficits associated with neurological conditions such as stroke[4]. Cognitive training has also been suggested to enhance general higher-order cognitive functioning in healthy populations, including emotion regulation[5,6]. However, meta-analytic evidence raises questions on the overall effectivity of such computerized cognitive training programs in healthy populations[7,8] and in populations with mild cognitive impairments[9]. Cognitive training in these populations has not consistently been shown to improve cognitive performance beyond the task that is being trained[7,8] or to yield significantly different effects than active control interventions (e.g., unstructured conversation sessions)[9]. The main limitation of stand-alone cognitive training interventions is the lack of generalization of performance improvements to non-trained cognitive skills in other contexts.

Yet, the working model of this thesis relied on the assumption that effects of tDCS on inhibitory control or working memory performance would generalize to the function of downregulating stress reactions. However, it could be that combining tDCS with cognitive training merely facilitates the effect of cognitive training itself. This would imply that no generalization effect could be expected. If so, functions like emotion regulation might be better facilitated by directly combining tDCS with emotion regulation exercises rather than combining tDCS with the computerized cognitive training as used in the studies of this thesis.

2. Prefrontal cortex activity in a complex dynamic system

In this thesis, upregulating excitability in the PFC was proposed to facilitate the cognitive flexibility that is needed for effective top-down stress regulation. However, aiming to upregulate excitability in PFC regions is not always an appropriate method to target pathological anxiety or prevent stress-related impairments of cognitive flexibility. For example, the PFC is not only involved in top-down regulation of anxiety, but also in top-down expression of anxiety such as avoidance behavior and the experience of negative emotions[10]. In pathological anxiety, increased PFC activity has been implicated in maladaptive forms of emotion regulation, including over-evaluating potential threats and excessive worry[11,12]. Increasing neural excitability in the PFC could therefore in some cases also have the opposite effect on stress reactivity, as is for example illustrated by the TMS study of Balderston and coworkers that resulted in enhanced threat responses, see Box 7.2.

Moreover, the Introduction (**Chapter 1**) shortly discussed the disruption of PFC functioning during extreme stress. This disruption could imply that the advantage of upregulating PFC excitability may be abolished when the same PFC regions get deactivated or disconnected from other regions in their neural network under the influence of severe stress[13–15]. In fact, the disruption of higher-order cognition during severe stress is one of the reasons why it is common military practice to train 'skills and drills' so extensively that the most essential actions become automated[16]. Hence, in very stressful situations, modulating excitability of the stress-sensitive PFC regions may not be an effective to maintain cognitive flexibility during operational performance.

Box 7.2. An example of *increasing* anxiety with prefrontal stimulation

Balderston and coworkers have performed a series of studies on the neural mechanisms underlying anxiety. They used the NPU threat-of-shock test (see also **Chapter 5**) and found that participants who were more anxious during threat-of-shock showed significantly lower right DLPFC activity during threat-of-shock[98]. This led to the hypothesis that lower threat-related right DLPFC activity underlies reduced top-down regulation of anxiety-like symptoms. Balderston et al. then performed another study testing this hypothesis by applying 10 Hz (excitatory) repetitive TMS over the right DLPFC[99]. Contrary to their hypothesis, however, results showed that TMS *increased* anxious responses to threat-of-shock. The authors pointed out that the association between right PFC activity and vigilant attention[10] may explain why TMS facilitated the increase in anxious arousal.

3. The linear translation of brain activity to tDCS protocols

The rationale behind anodal tDCS is often to enhance neural excitability of superficial cortical areas, with study designs that are largely based on findings from functional magnetic resonance imaging (fMRI) studies. For example, veterans with PTSD showed hypoactivity in the right inferior frontal gyrus in a previous fMRI study[17], driving the choice to apply anodal tDCS over this area (**Chapter 3**). The working model of this approach is somewhat simplified and does not specifically take into account that PFC activity reflects complex interactions with almost all other parts of the brain[18], and that fMRI-based changes in local blood flow are non-linearly related to local neural activity[19]. These complex interactions and non-linear relations imply that upregulating activity in a brain region based on fMRI-derived hypoactivity does not necessarily augment the associated behavioral or clinical outcome[20]. Hence, it would not in all cases be appropriate to linearly translate fMRI-based findings of cortical activation to tDCS protocols that aim to probe activity of a neural pathway.

Taken together, the present working model of improving top-down stress regulation by targeting PFC activity with anodal tDCS combined with cognitive training has several drawbacks. These drawbacks may limit the suitability of this approach to target several aspects of anxiety- and stress-related mental health.

In addition, a number of simplifications in the adopted working model of tDCS have been challenged. This raises further uncertainties regarding the suitability of the tDCS approach in the studies of this thesis, as will be discussed in the next section.

THE LIMITED MECHANISTIC UNDERSTANDING OF TDCS

"In God we trust. All others must bring data." – William Edwards Deming

Over the past years, the assumed cognitive effects of tDCS have been critically reviewed in a number of overview papers. One of those papers was written by Bestmann and coworkers in 2015[20]. They noticed (Page 13) that "Mounting evidence suggests that tES (transcranial electrical stimulation) can have a role in altering brain activity in a way that could be beneficial in health and disease." However, they also observed, with a deliberate ironic tone, that "Reports of such improvements, or neuroenhancement, span a surprisingly wide range of cognitive processes and a perplexing variety of neuropsychiatric disorders." Their point was that the countless number of studies suggesting that tDCS alters behavior contrasts the limited mechanistic understanding of *how* tDCS modulates neurophysiology and subsequently alters behavior. One of the issues they address is that "Applying an electrical field to a dynamic electrochemical system like the brain seems likely to have myriad nontrivial effects that preclude simple extrapolation onto behaviour." (Page 13)

Hence, in addition to gaps in knowledge of how the brain works and how brain activity relates to behavior, the gaps in knowledge of how tDCS modulates brain and behavioral processes may hinder the development of effective tDCS protocols. With the quote of Deming in mind, one may wonder whether also the present work relied too heavily on assumptions about the effects of tDCS that were not sufficiently supported by the available evidence. The following paragraphs discuss some of the gaps in knowledge related to the neurophysiological, behavioral and state- and trait dependent mechanisms involved in tDCS.

Gaps in the mechanistic understanding of neurophysiological effects

The conventional working model of the polarity-dependent effects of tDCS (anodal tDCS facilitates cortical excitability and cathodal tDCS inhibits cortical excitability) finds its basis in the observed effects of tDCS over the primary motor cortex on corticospinal excitability[21]. Whereas this model is convenient to work with, the extrapolation to other neural pathways and neural processes rests on assumptions that are not always supported by empirical evidence[22].

The neurophysiological effects of the electric field entering the cortex are debated or unclear on several aspects. For instance, anodal stimulation (inward current flow) is assumed to have an excitatory effect because it depolarizes the soma of aligned neural cells. However, the electric field simultaneously hyperpolarizes the dendrites, which would inhibit post-synaptic excitability[23]. A related aspect is illustrated in **Figure 7.1**. The direction of the current flow with respect to the cortical surface is opposite on different sites the same gyrus. It remains largely unclear how such a mix of inward and outward current flow influences the output of a cortical region. There are indications that inward current flow has stronger effects on neural excitability than outward current flow[24]. If so, the effects of "anodal stimulation", which was used in the studies in this thesis, should be stronger than "cathodal stimulation". Accordingly, there is evidence that anodal tDCS over the PFC has stronger effects on cognitive outcomes than cathodal tDCS[25]. This would support our hypothesis that anodal stimulation could facilitate overall neural activity in the targeted areas of the PFC. However, further research is warranted to gain better insight in this very basis of tDCS-effects.

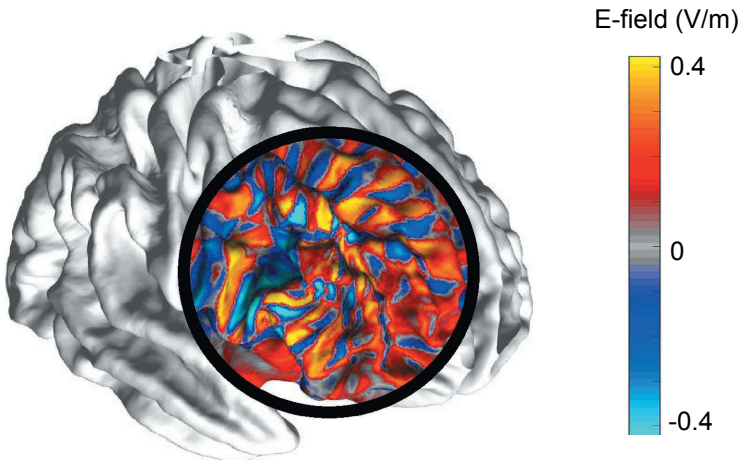


Figure 7.1. Simulated image showing the average tDCS electrical current flow direction with respect to the cortical surface orientation. The depicted image is focused on the right lateral prefrontal cortex – the tDCS-target area in our studies. Yellow-red colors (positive values) reflect current flowing into the cortical layer, blue colors (negative numbers) reflect current flowing out of the cortical layer. The image is simulated based on the electrode montage used in **Chapter 5** and **6** (2 mA; anode over the right DLPFC, F3; cathode over the parietal area, behind C2) with SimNIBS 3.2.3[31]. The image reflects the average of twenty simulations on twenty different brains derived from a publicly available MRI dataset of neurologically healthy individuals[32].

Gaps in the mechanistic understanding of behavioral effects of tDCS

Cognitive performance is the most popular way to measure the effects of prefrontal tDCS. Accordingly, there are indications that tDCS over specific areas of the PFC effectively modulates behavioral outcomes that are linked to those areas. For example, as referred to already in previous

chapters, a meta-analytic study by Wischnewski and coworkers nicely shows that tDCS over a central part of the DLPFC effectively modulates working memory performance[26]. However, there is still surprisingly little known about how tDCS induces such behavioral effects. In fact, although the main theoretical frameworks that aim to explain the effects of tDCS on behavior (see Box 7.3) are not mutually exclusive, they would in some cases predict quite different outcomes. For example, the activity-selective framework would predict that tDCS mainly facilitates ongoing synaptic plasticity (e.g., when learning new skills)[3,27], while the stochastic resonance framework would predict that tDCS mainly facilitates well-trained skills where the neural signal is already strong relative to background neural noise[28]. Alternatively, frameworks like the inhibition/excitation model[29] do not assume such directional relationships between tDCS and behavioral outcomes, but instead propose that the direction of tDCS-effects (excitatory or inhibitory) depends on what is "needed" at that moment to maintain the excitation/inhibition balance.

Box 7.3 Theoretical frameworks of electricity-induced stimulation of behavior

Several theoretical frameworks try to explain how effects of tDCS on cortical excitability translate into behavioral outcomes. The main frameworks according to Bestmann and coworkers[20] are summarized below.

- The **activity-selective framework** has been fundamental in the studies in this thesis, and poses that subthreshold effects of tDCS on neural excitability are only strong enough to influence active neural pathways, where it can facilitate or inhibit activity depending on the direction of current flow[3].
- The **input-bias framework** assumes that neural systems have multiple "states" or can gate between multiple pathways, and that tDCS can "switch" this system to a different state or bias information flow through a different pathway[3].
- The **inhibition/excitation framework** poses that neural systems function optimally when excitation and inhibition are balanced. TDCS is thought to shift this balance by adding some excitatory or inhibitory input[29]. Depending on whether this shift bring the excitation/inhibition balance closer or further away from the optimum, the output of the neural system will improve or deteriorate.
- The **zero-sum framework** poses that there is a finite amount of neural processing power in the brain[100]. As a consequence, every gain in neural processing power in one place means a loss of neural processing power elsewhere.
- The **stochastic resonance framework** refers to increasing the fidelity of a neuron or circuit by introducing small amounts of random noise (variability)[28]. A little bit of noise can drive low-level signals to a threshold. The stochastic resonance model therefore poses that techniques like tDCS inject low-level noise into a targeted brain area, thus increasing the responsiveness of the system, and thereby facilitating neural functioning.

To date, there is no consensus on the complementary explanatory value of these frameworks or which framework best accounts for the observed tDCS effects. Hence, gaining more insight in such fundamental mechanisms of tDCS seems to be critical to allow the development of valid hypotheses with directional predictions about the effects of a tDCS protocol on behavioral outcomes.

Remarkably, however, all these frameworks have one thing in common: the effect of tDCS is primarily conceptualized as a *nonspecific* influence on the brain, and the *specificity* of tDCS-effects on a behavioral process are conceptualized to depend on endogenous neural activity. In other words, the state of endogenous neural activity is identified as an essential factor in shaping the effect of tDCS. This brings us to another important point, namely, the state- and trait-dependency of tDCS-effects.

Gaps in the mechanistic understanding of state- and trait dependency

One of the most well-known and intuitive reasons for inter-individual variability in tDCS-effects is illustrated in **Figure 7.2**; the electric field strength and location depends on individual anatomy[30]).

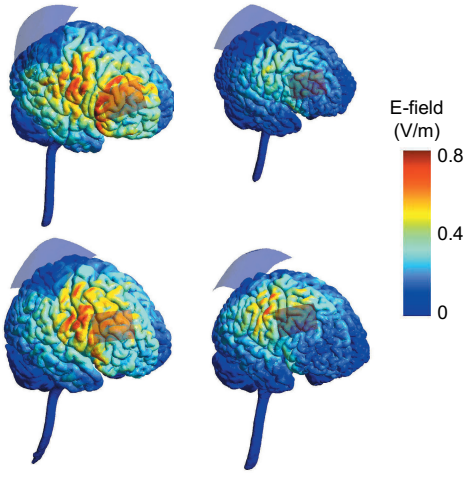


Figure 7.2: Example of electrical field distributions on four individual brains. The electrical fields are simulated in SimNIBS 3.2.3[31] based on 2 mA direct current stimulation with a 3x3 cm anode over F4 and a 5x7 cm cathode over C2 (electrode montage in **Chapter 5** and **6**). The brain models are obtained from a publicly available MRI dataset of neurologically healthy individuals[32] (here depicted: sub04, sub05, sub07 and sub11). This figure was originally published in *'Perspectives on Promises and Challenges of Electrical Brain Stimulation to Improve Stress Regulation in the Military' (MP-HFM-334-03), as Symposium Proceedings of the NATO symposium 'Applying Neuroscience to Performance: From Rehabilitation to Human Cognitive Augmentation' (STO-MP-HFM-334).*

The involvement of trait- and state-factors in the outcome of tDCS has been discussed in previous chapters. Particularly the results of exploratory analyses in **Chapter 5** underlined the importance of inter-individual variability in tDCS-effects. Analyzing the outcome of tDCS without taking such factors into account may not do justice to the technique and what we know of its mechanisms of action. One state factor that has a specific relevance to the present work, and could influence the outcome of tDCS, is stress.

Stress has a significant impact on PFC excitability and brain plasticity, as shortly discussed in the introduction (**Chapter 1**). The influence of stress on PFC excitability shows an inverted-U-shape, with mild stress (e.g., alertness) enhancing PFC excitability, while too much (e.g., panic) or too little stress (e.g., fatigue) reduces PFC excitability[14]. Moreover, stress responses are aimed at maintaining or restoring homeostasis of the bodily system, and flexibly adapting behavior in response to stress plays an important role in achieving homeostasis. This behavioral flexibility has been associated with flexibility in cortical excitability and plasticity levels that dynamically vary to keep levels of neural excitability within a functional range (so-called homeostatic plasticity)[33]. Accordingly, fearful relative to neutral stimuli have been shown to enhance the effect of TMS on motor evoked potentials[34,35], suggesting that corticospinal excitability is increased by anxiety-related arousal, e.g., to be prepared for motor actions. Homeostatic mechanisms could likewise reduce or even reverse effects of non-invasive brain stimulation on cortical excitability and plasticity, for example to prevent further increases in cortical excitability when excitability levels are already high[33]. The strength and direction of tDCS-effects on cortical excitability and plasticity may thus be shaped by the level of stress (arousal) as well as by homeostatic mechanisms.

With respect to effects of prefrontal tDCS, this idea has received support from several studies. For example, anodal tDCS over the left DLPFC did not show any effect on working memory performance after mild stress was induced (by the socially evaluated cold pressor test[36]. Results of two other studies indicated that anodal tDCS over the right or left DLPFC even impaired cognitive performance on working memory or attention tasks when arousal levels were high (i.e., after the Trier Social Stress Test[37], or based on pupil dilation and state anxiety assessments[38]). These findings suggest that the effects of anodal tDCS on DLPFC-dependent cognitive performance can be abolished by moderate levels of stress and reversed by high levels of stress.

Hence, although still speculative, the behavioral outcomes of tDCS may crucially depend on the neurophysiological effects of stress and homeostatic plasticity. Considering the central role of stress and the alterations in stress mechanisms involved in disorders like PTSD and anxiety, “stress state” may have an important impact on the behavioral and clinical effects of non-invasive brain stimulation in this context.

Taken together, this section discussed several gaps in the mechanistic understanding of effects of tDCS applied to the PFC on stress-related behavioral outcomes. Such sources of

variability and uncertainty surrounding non-invasive brain stimulation methods may be one of the reasons why a substantial body of studies, including our own, found no significant effects of tDCS via the hypothesized mechanisms.

Future studies on non-invasive brain stimulation may therefore benefit from focusing on other methods that circumvent or take into account these sources of variability and uncertainty. The next section presents several potential directions for further research on the clinical utility of non-invasive brain stimulation in relation to stress-related mental health.

FUTURE DIRECTIONS

BACK TO THE DRAWING TABLE

How to determine tDCS-effects on excitability in prefrontal pathways?
The outcome of prefrontal tDCS may be better predicted when tDCS-induced changes in PFC excitability would be more directly measures. For example, tDCS effects on the primary motor cortex (hand area) can be measured quite directly by quantifying corticospinal excitability based on the motor-evoked potential amplitude[39]. Developing similar readouts for cortical excitability has been attempted for somatosensory, visual, auditory and frontal regions[25,40–45]. These attempts are mainly based on solutions with real-time neuroimaging with fMRI or EEG. For example, cortical excitability could be derived from TMS-evoked potentials in the EEG signals from the targeted cortical area (see e.g.,[40,45,46]). Such readouts of PFC excitability could further improve understanding on the fundamental neurophysiological effects of a tDCS protocol. For example, supporting the parallels between primary motor cortex stimulation and PFC stimulation, EEG-derived TMS-evoked potentials elicited by TMS pulses to M1 and to the PFC (middle frontal gyrus) were shown to strongly correlate[47]. On the other hand, some of the challenges posed by the sources of variability and uncertainty surrounding tDCS would remain, such as predicting the consequences of tDCS beyond regional cortical excitability.

INFORMED BY FUNCTIONAL CONNECTIVITY

While the studies of this thesis focused on stimulating a single brain region, brain regions do not act in isolation. The outcome of tDCS is also shaped by the input and output of the tDCS-targeted region. Therefore, taking into account functional connectivity of neural circuits can provide better insight in the effects of tDCS[48]. Drawing a parallel to TMS research in the domain of depression, the antidepressant efficacy of rTMS over the DLPFC has been associated with functional connectivity between the DLPFC and the subgenual anterior cingulate cortex[49–52]. The extent to which a standard rTMS treatment targeted a region in the DLPFC that was functionally connected to the sgACC has been shown to predict the antidepressant efficacy[50] (but note that this may not apply to all depressive subgroups, considering, for example, the negative results from a large RCT in China[53]). In addition, it has been shown to be feasible to detect the individual TMS target location in the MR scanner that optimally activates the

DLPFC-sgACC connection[54,55]. Brain stimulation targets could effectively be personalized using such methods, which may increase clinical effectivity. With respect to tDCS and higher-order cognitive functions like working memory, connectivity within the frontoparietal executive control network (including the DLPFC) plays an important role. Prefrontal tDCS has been shown to significantly influence functional connectivity within this network[56]. A recent study suggested that this effect is stronger when the tDCS protocol (e.g., the electrode montage) is adapted to the functional nodes of this network[57]. However, fMRI-based personalization is costly. Exploratory results of **Chapter 5** showed that the effect of tDCS on working memory significantly depends on neural cross-talk reflected in the EEG theta/beta power ratio, which may provide a more feasible method for functional connectivity readouts to guide personalized tDCS protocols to target higher-order cognitive functions.

TARGETING NETWORKS

Along these lines, approaching tDCS from a network perspective is gaining ground (see e.g.,[58,59]). A network perspective may also do more justice to the brain dynamics underlying adaptive coping with stress. For example, stress-induced downregulation of DLPFC activity is actually part of a larger-scale loss of connectivity within the whole frontoparietal executive network, in favor of higher activity in the salience network (including regions like the amygdala and insula, subserving threat responding)[15,60].

The potential of stimulating neural oscillations

Instead of monotonic modulation of neural excitability with tDCS, targeting neural network activity may be more effective with non-invasive brain stimulation techniques that modulate neural oscillations. Oscillations play an important role in the communication between brain regions within a network and synaptic plasticity[61]. A technique related to tDCS is transcranial alternating current stimulation (tACS). With tACS, the electric field that is applied over the scalp oscillates in a specific frequency. Evidence from animal and human studies has shown that this exogenous oscillating field can enhance endogenous neural oscillations of the same frequency[62]. As a result, tACS has been shown to modulate cognitive processes that are linked to neural oscillations in that frequency[63–65].

With respect to treatment of stress-related disorder like anxiety and PTSD, memory forms an important cognitive process underlying evidence-based exposure therapy[66,67]. Neural oscillations in the theta frequency (4-8 Hz) have been strongly linked to memory formation and consolidation[61,68]. Theta oscillations are assumed to coordinate the communication between hubs of the (fear) memory network, including the medial PFC, hippocampus and amygdala[69]. Increasing evidence suggests that rhythmic brain stimulation in the theta rhythm has a positive effect on memory processes[65]. Targeting theta activity in the fear memory network with tACS may therefore be a promising way to boost memory processes underlying the effects of exposure-based therapy for PTSD.

Another interesting idea has been raised by Clancy and coworkers. They investigated filtering of sensory input, a process linked to posterior alpha oscillations. Disturbed sensory filtering is thought lead to symptoms of intrusive re-experiencing and hyperarousal in PTSD patients, and has been associated with dysregulated alpha activity[70,71]. A study in healthy volunteers showed that multisession alpha rhythm tACS can enhance functional connectivity in the alpha range and reduce anxious arousal[72]. Targeting alpha activity with tACS may therefore be a promising research avenue to target more implicit or bottom-up processes driving PTSD symptomatology.

Additionally, oscillatory brain stimulation protocols can be specifically adapted to brain states. For example, a recent study showed that a TMS pulse burst applied to the dorsomedial PFC had significant but opposite effects when applied during the upgoing or descending phase of a theta oscillation[73]. More specifically, TMS during the upgoing theta phase decreased theta synchronization, while TMS during the descending phase increased theta synchronization and associated working memory performance. Likewise, applying bursts of high-frequency gamma oscillations with tACS to the PFC have been show to enhance working memory performance, but only when applied during the peak of a theta wave, not when gamma bursts were applied during the theta trough[74].

These ideas illustrate that oscillatory brain stimulation, for example by tACS in the theta or alpha rhythm, may provide a way to modulate neural network activity in a brain-state-specific manner, and thereby target crucial cognitive processes in stress-related disorders like PTSD. Oscillatory brain stimulation may thereby provide a much more specific and perhaps more effective way to target brain processes linked to the clinical symptoms than tDCS.

CLINICAL AND ETHICAL IMPLICATIONS

CLINICAL IMPLICATIONS

Altogether, the mixed results and uncertainties about the effectivity of the tDCS approach used in this thesis suggest that such tDCS protocols are not yet ready for clinical application. However, it could be that clinical effects of tDCS require a much higher dose (e.g., more sessions). Yet, a dose-dependent efficacy is not directly supported by our results. In **Chapter 5**, we found no evidence for effects of tDCS after the first session, indicating that simply increasing the number of sessions would not have made any difference in the final results. Moreover, another study that applied tDCS with similar settings as in **Chapter 3** (anodal tDCS over right IFG combined with inhibitory control training), but with 15 sessions instead of the 5 sessions applied in our study, likewise showed no significant tDCS-effects on inhibitory control performance or clinical symptoms of ADHD[75,76]. Hence, at present our results provide no support for clinical tDCS applications in the domain of stress-related mental health. Nonetheless, considering a higher dose may be fruitful regarding tDCS protocols that show more promising effects (e.g., the combination of tDCS with virtual reality trauma exposure[77]).

For example, in TMS treatment for depression (typically 20-30 sessions[78]) it has been shown that some individuals require a much higher dose or longer treatment time than others to gain clinical effects[79]. This suggests that the initial response to non-invasive brain stimulation might highly vary between individuals, and that the therapeutic effects start to manifest or stabilize only after much higher dose than applied in our studies.

In contrast to tDCS, TMS has shown more positive results in the treatment of PTSD. Recent RCTs showed significant effects on PTSD symptom reduction after high- or low-frequency rTMS over the right DLPFC as a stand-alone treatment[80], in line with the level B evidence status ('probable efficacy') of TMS-treatment for PTSD[81]. However, while the pooled effects size of low-frequency and high-frequency rTMS protocols together is statistically significant (a standardized mean difference compared to sham rTMS of 1.1), the effect varies considerably between studies (95%-confidence interval of 2.10 to 0.15)[80]. Moreover, the efficacy of rTMS treatments in military personnel and veterans is not yet clear. While one RCT found positive effects of prefrontal rTMS on PTSD symptoms in veterans[82], another RCT showed no significant effects of prefrontal rTMS on depression symptoms in veterans, especially in case of comorbid PTSD[83].

What could improve the effectivity of rTMS treatments is the combination with psychotherapy[80,84]. Studies of prefrontal rTMS combined with PTSD or anxiety treatment sessions have suggested synergistic effects[77,85–88]. In fact, non-invasive brain stimulation has a specific clinical potential to enhance learning and memory processes that are involved in exposure-based psychotherapy for PTSD and anxiety[89]. Likewise, tDCS may provide an effective add-on method to enhance psychotherapeutic effects. However, more research in this domain is needed as robust evidence is still lacking for the benefit of combining psychotherapy with tDCS[84], and the combination of tDCS with methods of fear extinction in healthy research volunteers have shown mixed results[90].

ETHICAL CONSIDERATIONS REGARDING TDCS AND NEUROENHANCEMENT

The application of non-invasive brain stimulation to enhance cognitive functions have raised ethical concerns on health-related issues (are there adverse side effects on the long term?) and moral issues (does it make you a "different" person?), particularly in the context of military populations[91]. While these are important questions to consider, an ethical discussion is beyond the scope of this thesis. Yet, several considerations from neuroscientific and psychological perspectives may help to guide the approach of ethical concerns surrounding the use of tDCS in the domain of cognition and emotional behavior.

tDCS versus a double espresso

Ethical concerns about neuroenhancement with tDCS are largely theoretical. While tDCS could be capable of significantly enhancing cognitive functions beyond "normal" or "healthy" levels, robust evidence is lacking. For example, it may feel intuitive that tDCS has more capacity to restore a deficient process than to enhance an already efficient process, e.g., due to ceiling

effects. On the other hand, sometimes 'efficient' processes may be more sensitive to the effect of tDCS, as illustrated in Box 7.4. Nevertheless, the effectivity of tDCS both in psychiatric treatment and cognitive enhancement is still a topic of ongoing research. Therefore, at present, even enthusiastic perspectives on tDCS-neuroenhancement in the military are tempered by warnings that tDCS should not be used before robust evidence supports practically relevant effects of tDCS on military skills[92–95].

Box 7.4. tDCS to enhance efficiency vs. tDCS to restore deficiency

Some findings suggest that tDCS is mainly effective to restore deficient cognitive processes. For example, a recent study by Weidler and coworkers found significant effects of tDCS (single-session) on impulse control and impulsive aggression, but only in participants who showed impulse control problems (addiction to alcohol or tobacco use), not in healthy controls[101]. Interestingly, the study settings were very similar to the study described in **Chapter 3**; anodal tDCS was applied for 20 minutes at 1.5 mA over the right DLPFC with the return electrode over the left supraorbital area, the outcomes were assessed using the stop-signal task, and the participating patients also showed impulse control problems (although with a different diagnosis). This raises the question why Weidler et al. (2022)[101] found a significant tDCS-effect where we didn't. Although no definitive answer can be provided here, the idea that prefrontal tDCS is more effective in populations with cognitive deficiencies sounds intuitive and clinically appealing, but is not supported by our data. In fact, it might even be the other way around; we found indications in **Chapter 5** that the short-term effect of tDCS on working memory performance was stronger in healthy participants with better baseline performance. While other factors like younger age may also have played a role, these examples illustrate the mixed findings of cognitive enhancement by tDCS across healthy and clinical populations.

Yet, it is exactly on the boundary between restoring dysfunctional and enhancing functional brain processes that ethical questions are raised[96]. In that domain, however, the use of methods in the military to manipulate already functional brain or behavioral processes is not new. Some examples of accepted forms of behavioral or mental manipulations in the military include sleep deprivation, behavioral and social training interventions, physical exercise and nutritional intake[94]. The effect of non-invasive brain stimulation with tDCS on mental state and behavior is likely not fundamentally different from the effects of these interventions. The ethical side of tDCS or non-invasive brain stimulation in the military may therefore best be discussed in relation to the already existing methods for cognitive and behavioral enhancement.

CONCLUDING REMARKS

The studies of this thesis showed no clinically relevant effects of anodal tDCS over the prefrontal cortex during cognitive training on cognitive functioning or stress-related behavior in military personnel. These findings are discussed in light of the many sources of variability and uncertainty in tDCS outcomes. In the field of stress-related mental health, the

variability in tDCS outcomes is complemented by variability in symptom profiles (see, e.g., the publication by Galatzer-Levy and Bryant (2013)[97] with the striking title "636,120 ways to have posttraumatic stress disorder"). Finding the right combination of tDCS-related parameters and neural targets to improve adaptive coping with stress may thus be challenging. In order to better face this challenge, more fundamental insights in the mechanisms of action of tDCS are required. Approaching brain stimulation from a network perspective and focusing on neural oscillations is suggested to yield more promising avenues for future research of non-invasive brain stimulation.

REFERENCES

1. Wager TD, Davidson ML, Hughes BL, Lindquist MA, Ochsner KN. Prefrontal-Subcortical Pathways Mediating Successful Emotion Regulation. *Neuron*. 2008;59(6):1037-1050. doi:10.1016/j.neuron.2008.09.006

2. Kohn N, Eickhoff SB, Scheller M, Laird AR, Fox PT, Habel U. Neural network of cognitive emotion regulation — An ALE meta-analysis and MACM analysis. *Neuroimage*. 2014;87:345-355. doi:10.1016/j.neuroimage.2013.11.001

3. Bikson M, Rahman A. Origins of specificity during tDCS: anatomical, activity-selective, and input-bias mechanisms. *Frontiers in Human Neuroscience*. 2013;0(OCT):688. doi:10.3389/FNHUM.2013.00688

4. Rogers JM, Foord R, Stolwyk RJ, Wong D, Wilson PH. General and Domain-Specific Effectiveness of Cognitive Remediation after Stroke: Systematic Literature Review and Meta-Analysis. *Neuropsychology Review*. 2018;28(3):285-309. doi:10.1007/S11065-018-9378-4/TABLES/5

5. Schweizer S, Grahn J, Hampshire A, Mobbs D, Dalgleish T. Training the Emotional Brain: Improving Affective Control through Emotional Working Memory Training. *Journal of Neuroscience*. 2013;33(12):5301-5311. doi:10.1523/JNEUROSCI.2593-12.2013

6. Cohen N, Margulies DS, Ashkenazi S, et al. Using executive control training to suppress amygdala reactivity to aversive information. *Neuroimage*. 2016;125:1022-1031. doi:10.1016/J.NEUROIMAGE.2015.10.069

7. Simons DJ, Boot WR, Charness N, et al. Do "Brain-Training" Programs Work? *Psychological Science in the Public Interest, Supplement*. 2016;17(3):103-186. doi:10.1177/1529100616661983

8. Sala G, Gobet F. Cognitive Training Does Not Enhance General Cognition. *Trends in Cognitive Sciences*. 2019;23(1):9-20. doi:10.1016/J.TICS.2018.10.004

9. Bahar-Fuchs A, Martyr A, Goh AMY, Sabates J, Clare L. Cognitive training for people with mild to moderate dementia. *Cochrane Database of Systematic Reviews*. 2019;2019(3). doi:10.1002/14651858.CD013069.PUB2/MEDIA/CDSR/CD013069/IMAGE_N/NCD013069-CMP-003-21.PNG

10. Davidson RJ. Affective neuroscience and psychophysiology: Toward a synthesis. *Psychophysiology*. 2003;40(5):655-665. doi:10.1111/1469-8986.00067

11. Kenwood MM, Kalin NH, Barbas H. The prefrontal cortex, pathological anxiety, and anxiety disorders. *Neuropsychopharmacology 2021 47:1*. 2021;47(1):260-275. doi:10.1038/s41386-021-01109-z

12. Kalisch R, Gerlicher AMV. Making a mountain out of a molehill: On the role of the rostral dorsal anterior cingulate and dorsomedial prefrontal cortex in conscious threat appraisal, catastrophizing, and worrying. *Neuroscience & Biobehavioral Reviews*. 2014;42:1-8. doi:10.1016/J.NEUBIOREV.2014.02.002

13. Arnsten AFT. Stress weakens prefrontal networks: molecular insults to higher cognition. *Nature Neuroscience*. 2015;18(10):1376-1385. doi:10.1038/nn.4087

14. Arnsten AFT. Stress signalling pathways that impair prefrontal cortex structure and function. *Nature Reviews Neuroscience*. 2009;10(6):410-422. doi:10.1038/nrn2648

15. Hermans EJ, Henckens MJAG, Joëls M, Fernández G. Dynamic adaptation of large-scale brain networks in response to acute stressors. *Trends in Neurosciences*. 2014;37(6):304-314. doi:10.1016/J.TINS.2014.03.006

16. Kramer EH, van Bezooijen B, Delahaij R. Sensemaking during operations and incidents. *Managing Military Organizations: Theory and Practice*. Published online January 1, 2010:126-137. doi:10.4324/9780203857106-19/SENSEMAKING-OPERATIONS-INCIDENTS-ERIC-HANS-KRAMER-BART-VAN-BEZOOIJEN

17. van Rooij S, Rademaker A, Kennis M, Vink M, Kahn R, Geuze E. Impaired right inferior frontal gyrus response to contextual cues in male veterans with PTSD during response inhibition. *Journal of Psychiatry & Neuroscience*. 2014;39(5):330-338. doi:10.1503/jpn.130223

18. Miller EK, Cohen JD. An Integrative Theory of Prefrontal Cortex Function. *Annual Review of Neuroscience*. 2001;24(1):167-202. doi:10.1146/annurev.neuro.24.1.167

19. Hillman EMC. Coupling Mechanism and Significance of the BOLD Signal: A Status Report. *Annu Rev Neurosci*. 2014;37:161. doi:10.1146/ANNUREV-NEURO-071013-014111

20. Bestmann S, de Berker AO, Bonaiuto J. Understanding the behavioural consequences of noninvasive brain stimulation. *Trends in Cognitive Sciences*. 2015;19(1):13-20. doi:10.1016/J.TICS.2014.10.003

21. Cirillo G, di Pino G, Capone F, et al. Neurobiological after-effects of non-invasive brain stimulation. *Brain Stimulation*. 2017;10(1):1-18. doi:10.1016/j.brs.2016.11.009

22. Yavari F, Jamil A, Mosayebi Samani M, Vidor LP, Nitsche MA. Basic and functional effects of transcranial Electrical Stimulation (tES)—An introduction. *Neuroscience & Biobehavioral Reviews*. 2018;85:81-92. doi:10.1016/J.NEUBIOREV.2017.06.015

23. Reato D, Salvador R, Bikson M, et al. Principles of Transcranial Direct Current Stimulation (tDCS): Introduction to the Biophysics of tDCS. *Practical Guide to Transcranial Direct Current Stimulation*. Published online 2019:45-80. doi:10.1007/978-3-319-95948-1_2

24. Lafon B, Rahman A, Bikson M, Parra LC. Direct Current Stimulation Alters Neuronal Input/Output Function. *Brain Stimulation*. 2017;10(1):36-45. doi:10.1016/j.brs.2016.08.014

25. Jacobson L, Koslowsky M, Lavidor M. tDCS polarity effects in motor and cognitive domains: a meta-analytical review. *Experimental Brain Research*. 2012;216(1):1-10. doi:10.1007/s00221-011-2891-9

26. Wischnewski M, Mantell KE, Opitz A. Identifying regions in prefrontal cortex related to working memory improvement: A novel meta-analytic method using electric field modeling. *Neuroscience & Biobehavioral Reviews*. 2021;130:147-161. doi:10.1016/J.NEUBIOREV.2021.08.017

27. Kronberg G, Bridi M, Abel T, Bikson M, Parra LC. Direct Current Stimulation Modulates LTP and LTD: Activity Dependence and Dendritic Effects. *Brain Stimulation*. 2017;10(1):51-58. doi:10.1016/j.brs.2016.10.001

28. Miniussi C, Harris JA, Ruzzoli M. Modelling non-invasive brain stimulation in cognitive neuroscience. *Neuroscience & Biobehavioral Reviews*. 2013;37(8):1702-1712. doi:10.1016/J.NEUBIOREV.2013.06.014

29. Krause B, Márquez-Ruiz J, Cohen Kadosh R. HUMAN NEUROSCIENCE MINI REVIEW ARTICLE The effect of transcranial direct current stimulation: a role for cortical excitation/inhibition balance? Published online 2013. doi:10.3389/fnhum.2013.00602

30. Opitz A, Paulus W, Will S, Antunes A, Thielscher A. Determinants of the electric field during transcranial direct current stimulation. *Neuroimage*. 2015;109:140-150. doi:10.1016/J.NEUROIMAGE.2015.01.033

31. Thielscher A, Antunes A, Saturnino GB. Field modeling for transcranial magnetic stimulation: A useful tool to understand the physiological effects of TMS? In: *2015 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*. IEEE; 2015:222-225. doi:10.1109/EMBC.2015.7318340

32. Hanke M, Baumgartner FJ, Ibe P, et al. A high-resolution 7-Tesla fMRI dataset from complex natural stimulation with an audio movie. *Scientific Data 2014 1:1*. 2014;1(1):1-18. doi:10.1038/sdata.2014.3

33. Schutter DJLG, Wischnewski M, Bekkering H. Stability through variability: Homeostatic plasticity and psychological resilience. *Behavioral and Brain Sciences*. 2015;38:e118. doi:10.1017/S0140525X14001678

34. Schutter DJLG, Hofman D, van Honk J. Fearful faces selectively increase corticospinal motor tract excitability: A transcranial magnetic stimulation study. *Psychophysiology*. 2008;45(3):345-348. doi:10.1111/j.1469-8986.2007.00635.x

35. Coombes SA, Tandonnet C, Fujiyama H, Janelle CM, Cauraugh JH, Summers JJ. Emotion and motor preparation: A transcranial magnetic stimulation study of corticospinal motor tract excitability. *Cognitive, Affective, & Behavioral Neuroscience 2009 9:4*. 2009;9(4):380-388. doi:10.3758/CABN.9.4.380

36. Friehs MA, Frings C. Evidence Against Combined Effects of Stress and Brain Stimulation on Working Memory. *Open Psychology*. 2020;2(1):40-56. doi:10.1515/psych-2020-0004

37. Ankri YLE, Braw Y, Luboshits G, Meiron O. The effects of stress and transcranial direct current stimulation (tDCS) on working memory: A randomized controlled trial. *Cognitive, Affective and Behavioral Neuroscience*. 2020;20(1):103-114. doi:10.3758/S13415-019-00755-7/FIGURES/5

38. Esposito M, Ferrari C, Fracassi C, Miniussi C, Brignani D. Responsiveness to left-prefrontal tDCS varies according to arousal levels. *European Journal of Neuroscience*. 2022;55(3):762-777. doi:10.1111/EJN.15584

39. di Lazzaro V, Ziemann U. The contribution of transcranial magnetic stimulation in the functional evaluation of microcircuits in human motor cortex. *Frontiers in Neural Circuits*. 2013;0(JAN):18. doi:10.3389/FNCIR.2013.00018/BIBTEX

40. Romero Lauro LJ, Rosanova M, Mattavelli G, et al. TDCS increases cortical excitability: Direct evidence from TMS–EEG. *Cortex*. 2014;58:99-111. doi:10.1016/J.CORTEX.2014.05.003

41. Antal A, Paulus W, Nitsche MA. Electrical stimulation and visual network plasticity. *Restorative Neurology and Neuroscience*. 2011;29:365-374. doi:10.3233/RNN-2011-0609

42. Zaehle T, Beretta M, Jäncke L, Herrmann CS, Sandmann P. Excitability changes induced in the human auditory cortex by transcranial direct current stimulation: Direct electrophysiological evidence. *Experimental Brain Research*. 2011;215(2):135-140. doi:10.1007/S00221-011-2879-5/FIGURES/3

43. Sugawara K, Onishi H, Yamashiro K, et al. The effect of anodal transcranial direct current stimulation over the primary motor or somatosensory cortices on somatosensory evoked magnetic fields. *Clinical Neurophysiology*. 2015;126(1):60-67. doi:10.1016/J.CLINPH.2014.04.014

44. Dieckhöfer A, Waberski TD, Nitsche M, Paulus W, Buchner H, Gobbelé R. Transcranial direct current stimulation applied over the somatosensory cortex – Differential effect on low and high frequency SEPs. *Clinical Neurophysiology*. 2006;117(10):2221-2227. doi:10.1016/J.CLINPH.2006.07.136

45. Bai Y, Xia X, Kang J, Yang Y, He J, Li X. TDCS modulates cortical excitability in patients with disorders of consciousness. *NeuroImage: Clinical*. 2017;15:702-709. doi:10.1016/J.NICL.2017.01.025

46. Casarotto S, Canali P, Rosanova M, et al. Assessing the effects of electroconvulsive therapy on cortical excitability by means of transcranial magnetic stimulation and electroencephalography. *Brain Topography*. 2013;26(2):326-337. doi:10.1007/S10548-012-0256-8/FIGURES/2

47. Kähkönen S, Komssi S, Wilenius J, Ilmoniemi RJ. Prefrontal TMS produces smaller EEG responses than motor-cortex TMS: Implications for rTMS treatment in depression. *Psychopharmacology (Berl)*. 2005;181(1):16-20. doi:10.1007/S00213-005-2197-3/FIGURES/3

48. Hordacre B, Moezzi B, Ridding MC. Neuroplasticity and network connectivity of the motor cortex following stroke: A transcranial direct current stimulation study. *Human Brain Mapping*. 2018;39(8):3326-3339. doi:10.1002/HBM.24079

49. Siddiqi SH, Weigand A, Pascual-Leone A, Fox MD. Identification of Personalized Transcranial Magnetic Stimulation Targets Based on Subgenual Cingulate Connectivity: An Independent Replication. *Biological Psychiatry*. 2021;90(10):e55-e56. doi:10.1016/J.BIOPSYCH.2021.02.015

50. Fox MD, Buckner RL, White MP, Greicius MD, Pascual-Leone A. Efficacy of Transcranial Magnetic Stimulation Targets for Depression Is Related to Intrinsic Functional Connectivity with the Subgenual Cingulate. *Biological Psychiatry*. 2012;72(7):595-603. doi:10.1016/J.BIOPSYCH.2012.04.028

51. Cash RFH, Zalesky A, Thomson RH, Tian Y, Cocchi L, Fitzgerald PB. Subgenual Functional Connectivity Predicts Antidepressant Treatment Response to Transcranial Magnetic Stimulation: Independent Validation and Evaluation of Personalization. *Biological Psychiatry*. 2019;86(2):e5-e7. doi:10.1016/J.BIOPSYCH.2018.12.002

52. Oathes D. Depression Improvement From rTMS Facilitated by Subgenual Cingulate Engagement Indexed by Interleaved TMS/fMRI. *Biological Psychiatry*. 2021;89(9):S261-S262. doi:10.1016/J.BIOPSYCH.2021.02.654

53. Hopman HJ, Chan SMS, Chu WCW, et al. Personalized prediction of transcranial magnetic stimulation clinical response in patients with treatment-refractory depression using neuroimaging biomarkers and machine learning. *Journal of Affective Disorders*. 2021;290:261-271. doi:10.1016/J.JAD.2021.04.081

54. Vink JJT, Mandija S, Petrov PI, van den Berg CAT, Sommer IEC, Neggers SFW. A novel concurrent TMS-fMRI method to reveal propagation patterns of prefrontal magnetic brain stimulation. *Human Brain Mapping*. 2018;39(11):4580-4592. doi:10.1002/HBM.24307

55. Duprat R, Linn K, Satterthwaite T, et al. Functional connectivity as a tool to individualize DLPFC targeting in TMS. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation*. 2019;12(2):529. doi:10.1016/J.BRS.2018.12.742

56. Chan MMY, Yau SSY, Han YMY. The neurobiology of prefrontal transcranial direct current stimulation (tDCS) in promoting brain plasticity: A systematic review and meta-analyses of human and rodent studies. *Neuroscience & Biobehavioral Reviews*. 2021;125:392-416. doi:10.1016/j.neubiorev.2021.02.035

57. Soleimani G, Kupliki R, Bodurka J, Paulus MP, Ekhtiari H. How structural and functional MRI can inform dual-site tACS parameters: A case study in a clinical population and its pragmatic implications. *Brain Stimulation*. 2022;15(2):337-351. doi:10.1016/J.BRS.2022.01.008

58. To WT, de Ridder D, Hart J, Vanneste S. Changing brain networks through non-invasive neuromodulation. *Frontiers in Human Neuroscience*. 2018;12:128. doi:10.3389/FNHUM.2018.00128/BIBTEX

59. Kim K, Ekstrom AD, Tandon N. A network approach for modulating memory processes via direct and indirect brain stimulation: Toward a causal approach for the neural basis of memory. *Neurobiology of Learning and Memory*. 2016;134(Part A):162-177. doi:10.1016/J.NLM.2016.04.001

60. Young CB, Raz G, Everaerd D, et al. Dynamic Shifts in Large-Scale Brain Network Balance As a Function of Arousal. *Journal of Neuroscience*. 2017;37(2):281-290. doi:10.1523/JNEUROSCI.1759-16.2016

61. Fell J, Axmacher N. The role of phase synchronization in memory processes. *Nature Reviews Neuroscience 2011 12:2*. 2011;12(2):105-118. doi:10.1038/nrn2979

62. Schutter DJLG. Syncing your brain: electric currents to enhance cognition. *Trends in Cognitive Sciences*. 2014;18(7):331-333. doi:10.1016/j.tics.2014.02.011

63. Elyamany O, Leicht G, Herrmann CS, Mulert C. Transcranial alternating current stimulation (tACS): from basic mechanisms towards first applications in psychiatry. *European Archives of Psychiatry and Clinical Neuroscience*. 2021;271(1):135-156. doi:10.1007/s00406-020-01209-9

64. Schutter DJLG, Wischnewski M. A meta-analytic study of exogenous oscillatory electric potentials in neuroenhancement. *Neuropsychologia*. 2016;86:110-118. doi:10.1016/j.neuropsychologia.2016.04.011

65. Klink K, Paßmann S, Kasten FH, Peter J. The Modulation of Cognitive Performance with Transcranial Alternating Current Stimulation: A Systematic Review of Frequency-Specific Effects. *Brain Sciences*. 2020;10(12):1-33. doi:10.3390/BRAINSCI10120932

66. Hamblen JL, Schnurr PP, Rosenberg A, Eftekhari A. A guide to the literature on psychotherapy for PTSD. *Psychiatric Annals*. 2009;39(6):348-354. doi:10.3928/00485713-20090515-02

67. Vervliet B, Craske MG, Hermans D. Fear Extinction and Relapse: State of the Art. Published online 2013. doi:10.1146/annurev-clinpsy-050212-185542

68. Herweg NA, Solomon EA, Kahana MJ. Theta Oscillations in Human Memory. *Trends in Cognitive Sciences*. 2020;24(3):208-227. doi:10.1016/J.TICS.2019.12.006

69. Çalışkan G, Stork O. Hippocampal network oscillations as mediators of behavioural metaplasticity: Insights from emotional learning. *Neurobiology of Learning and Memory*. 2018;154:37-53. doi:10.1016/J.NLM.2018.02.022

70. Clancy KJ, Albizu A, Schmidt NB, Li W. Intrinsic sensory disinhibition contributes to intrusive re-experiencing in combat veterans. *Scientific Reports 2020 10:1*. 2020;10(1):1-11. doi:10.1038/s41598-020-57963-2

71. Clancy K, Ding M, Bernat E, Schmidt NB, Li W. Restless 'rest': intrinsic sensory hyperactivity and disinhibition in post-traumatic stress disorder. *Brain*. 2017;140(7):2041-2050. doi:10.1093/BRAIN/AWX116

72. Clancy KJ, Baisley SK, Albizu A, Kartvelishvili N, Ding M, Li W. Lasting connectivity increase and anxiety reduction via transcranial alternating current stimulation. *Social Cognitive and Affective Neuroscience*. 2018;13(12):1305-1316. doi:10.1093/scan/nsy096

73. Gordon PC, Belardinelli P, Stenroos M, Ziemann U, Zrenner C. Prefrontal theta phase-dependent rTMS-induced plasticity of cortical and behavioral responses in human cortex. *Brain Stimulation*. 2022;15(2):391-402. doi:10.1016/J.BRS.2022.02.006

74. Alekseichuk I, Turi Z, Amador de Lara G, Antal A, Paulus W. Spatial Working Memory in Humans Depends on Theta and High Gamma Synchronization in the Prefrontal Cortex. *Current Biology*. 2016;26(12):1513-1521. doi:10.1016/j.cub.2016.04.035

75. Westwood SJ, Bozhilova N, Criaud M, et al. The effect of transcranial direct current stimulation (tDCS) combined with cognitive training on EEG spectral power in adolescent boys with ADHD: A double-blind, randomized, sham-controlled trial. *IBRO Neuroscience Reports*. 2022;12:55-64. doi:10.1016/J.IBNEUR.2021.12.005

76. Westwood SJ, Criaud M, Lam SL, et al. Transcranial direct current stimulation (tDCS) combined with cognitive training in adolescent boys with ADHD: a double-blind, randomised, sham-controlled trial. *Psychological Medicine*. Published online 2021:1-16. doi:10.1017/S0033291721001859

77. van 't Wout-Frank M, Shea MT, Larson VC, Greenberg BD, Philip NS. Combined transcranial direct current stimulation with virtual reality exposure for posttraumatic stress disorder: Feasibility and pilot results. *Brain Stimulation*. 2019;12(1):41-43. doi:10.1016/j.brs.2018.09.011

78. McClintock SM, Reti IM, Carpenter LL, et al. Consensus Recommendations for the Clinical Application of Repetitive Transcranial Magnetic Stimulation (rTMS) in the Treatment of Depression. *The Journal of Clinical Psychiatry*. 2018;79(1):35-48. doi:10.4088/JCP.16cs10905

79. Kaster TS, Downar J, Vila-Rodriguez F, et al. Trajectories of response to dorsolateral prefrontal rTMS in major depression: A three-D study. *American Journal of Psychiatry*. 2019;176(5):367-375. doi:10.1176/APPI.AJP.2018.18091096/SUPPL_FILE/APPI.AJP.2018.18091096.DS001.PDF

80. Belsher BE, Beech EH, Reddy MK, et al. Advances in repetitive transcranial magnetic stimulation for posttraumatic stress disorder: A systematic review. *Journal of Psychiatric Research*. 2021;138:598-606. doi:10.1016/J.JPSYCHIRES.2021.05.011

81. Lefaucheur JP, Aleman A, Baeken C, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014–2018). *Clinical Neurophysiology*. 2020;131(2):474-528. doi:10.1016/J.CLINPH.2019.11.002

82. Petrosino NJ, Wout-Frank M van 't, Aiken E, et al. One-year clinical outcomes following theta burst stimulation for post-traumatic stress disorder. *Neuropsychopharmacology*. 2020;45(6):940-946. doi:10.1038/s41386-019-0584-4

83. Yesavage JA, Fairchild JK, Mi Z, et al. Effect of Repetitive Transcranial Magnetic Stimulation on Treatment-Resistant Major Depression in US Veterans: A Randomized Clinical Trial. *JAMA Psychiatry*. 2018;75(9):884-893. doi:10.1001/JAMAPSYCHIATRY.2018.1483

84. Dedoncker J, Baeken C, de Raedt R, Vanderhasselt MA. Combined transcranial direct current stimulation and psychological interventions: State of the art and promising perspectives for clinical psychology. *Biological Psychology*. 2021;158:107991. doi:10.1016/J.BIOPSYCHO.2020.107991

85. Isserles M, Shalev AY, Roth Y, et al. Effectiveness of deep transcranial magnetic stimulation combined with a brief exposure procedure in post-traumatic stress disorder-a pilot study. *Brain Stimulation*. 2013;6(3):377-383. doi:10.1016/j.brs.2012.07.008

86. Osuch EA, Benson BE, Luckenbaugh DA, Geraci M, Post RM, McCann U. Repetitive TMS combined with exposure therapy for PTSD: a preliminary study. *J Anxiety Disord*. 2009;23(1):54-59. doi:10.1016/j.janxdis.2008.03.015

87. Kozel FA, Motes MA, Didehbani N, et al. Repetitive TMS to augment cognitive processing therapy in combat veterans of recent conflicts with PTSD: A randomized clinical trial. *Journal of Affective Disorders*. 2018;229:506-514. doi:10.1016/j.jad.2017.12.046

88. Herrmann MJ, Katzorke A, Busch Y, et al. Medial prefrontal cortex stimulation accelerates therapy response of exposure therapy in acrophobia. *Brain Stimulation*. 2017;10(2):291-297. doi:10.1016/j.brs.2016.11.007

89. Marin MF, Camprodon J a., Dougherty DD, Milad MR. Device-based brain stimulation to augment fear extinction: Implications for ptsd treatment and beyond. *Depression and Anxiety*. 2014;31(4):269-278. doi:10.1002/da.22252

90. Faucher CR, Doherty RA, Philip NS, Harle ASM, Cole JJE, Wout-Frank M van't. Is There a Neuroscience-Based, Mechanistic Rationale for Transcranial Direct Current Stimulation as an Adjunct Treatment for Posttraumatic Stress Disorder? *Behavioral Neuroscience*. 2021;135(6):702-713. doi:10.1037/BNE0000487

91. Sehm B, Ragert P. Why non-invasive brain stimulation should not be used in military and security services. *Frontiers in Human Neuroscience*. 2013;7(SEP). doi:10.3389/FNHUM.2013.00553

92. Davis SE, Smith GA. Transcranial Direct Current Stimulation Use in Warfighting: Benefits, Risks, and Future Prospects. *Frontiers in Human Neuroscience*. 2019;13:114. doi:10.3389/fnhum.2019.00114

93. Levasseur-Moreau J, Brunelin J, Fecteau S. Non-invasive brain stimulation can induce paradoxical facilitation. Are these neuroenhancements transferable and meaningful to security services? *Frontiers in Human Neuroscience*. 2013;0(JUL):449. doi:10.3389/FNHUM.2013.00449

94. Brunyé TT, Brou R, Tracy &, et al. A Review of US Army Research Contributing to Cognitive Enhancement in Military Contexts. *Journal of Cognitive Enhancement 2020 4:4*. 2020;4(4):453-468. doi:10.1007/S41465-020-00167-3

95. Feltman KA, Hayes AM, Bernhardt KA, Nwala E, Kelley AM. Viability of tDCS in Military Environments for Performance Enhancement: A Systematic Review. *Military Medicine*. 2020;185(1-2):e53-e60. doi:10.1093/MILMED/USZ189

96. Jwa AS. Regulating the Use of Cognitive Enhancement: an Analytic Framework. *Neuroethics*. 2019;12(3):293-309. doi:10.1007/S12152-019-09408-5/TABLES/1

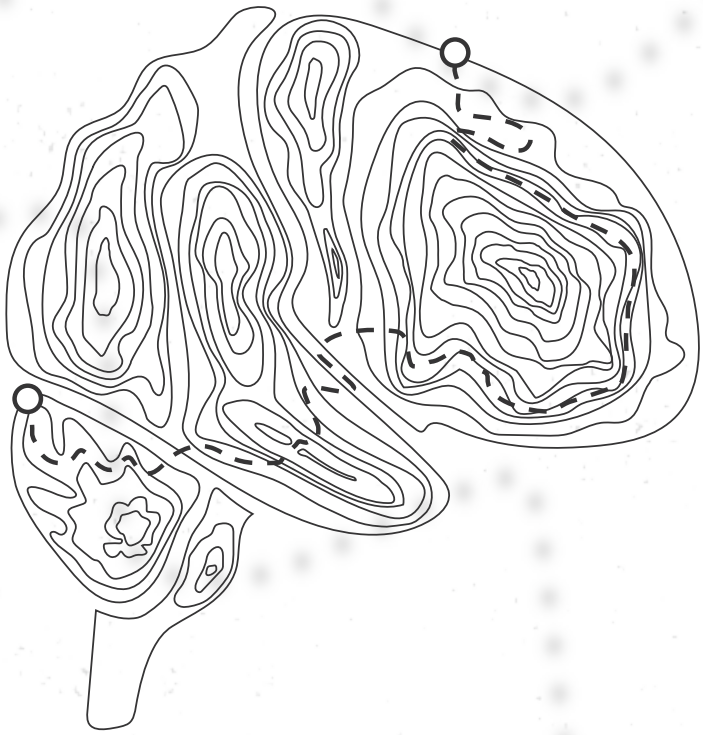
97. Galatzer-Levy IR, Bryant RA. 636,120 Ways to Have Posttraumatic Stress Disorder. *Perspectives on Psychological Science*. 2013;8(6):651-662. doi:10.1177/1745691613504115

98. Balderston NL, Liu J, Roberson-Nay R, Ernst M, Grillon C. The relationship between dlPFC activity during unpredictable threat and CO2-induced panic symptoms. *Translational Psychiatry*. 2017;7(12):1266. doi:10.1038/s41398-017-0006-5

99. Balderston NL, Beydler EM, Roberts C, et al. Mechanistic link between right prefrontal cortical activity and anxious arousal revealed using transcranial magnetic stimulation in healthy subjects. *Neuropsychopharmacology 2019 45:4*. 2019;45(4):694-702. doi:10.1038/s41386-019-0583-5

100. Brem AK, Fried PJ, Horvath JC, Robertson EM, Pascual-Leone A. Is neuroenhancement by noninvasive brain stimulation a net zero-sum proposition? *Neuroimage*. 2014;85:1058-1068. doi:10.1016/J.NEUROIMAGE.2013.07.038

101. Weidler C, Habel U, Wallheinke P, et al. Consequences of prefrontal tDCS on inhibitory control and reactive aggression. *Social Cognitive and Affective Neuroscience*. 2022;17(1):120-130. doi:10.1093/scan/nsaa158



APPENDICES

NEDERLANDSE SAMENVATTING

ACHTERGROND

Elektrische stimulatie van de hersenen: kan dat mentale gezondheidsproblemen verhelpen? Deze vraag bestaat al eeuwen. Het gebruik van bijvoorbeeld elektrische vissen om klachten zoals hoofdpijn te bestrijden stamt uit de tijd van de oude Romeinen. Op dit moment zijn elektroconvulsieve therapie (ECT) en diepe hersenstimulatie de meest bekende vormen van elektrische hersenstimulatie. Deze technieken worden nog altijd toegepast en verder ontwikkeld binnen de psychiatrie en neurologie. Daarnaast deed zich enkele decennia geleden een interessante nieuwe ontwikkeling voor: ook *niet-invasieve* technieken die de hersenen blootstellen aan elektrische stroom of magnetische pulsen vanuit buiten de schedel bleken in staat de hersenen op een gerichte manier te stimuleren. Deze niet-invasieve technieken zijn veilig en hebben nauwelijks bijwerkingen, en lenen zich daardoor voor bredere toepassingen.

De aanleiding van dit proefschrift is de potentiële toepassing van niet-invasieve hersenstimulatie op het vlak van mentale gezondheid bij militairen en veteranen. Militairen en veteranen hebben door blootstelling aan zeer stressvolle situaties en mogelijk traumatische gebeurtenissen een verhoogd risico op mentale gezondheidsklachten, zoals het ontwikkelen van angst, boosheids- en agressieklachten of een posttraumatische stressstoornis (PTSS). Bovendien bieden de huidige therapieën voor deze klachten, zoals psychologische traumabehandeling of medicatie, onvoldoende herstel voor een groot deel van de militairen en veteranen. Daarom is het van belang om voor deze populatie nieuwe preventie- en behandelmethoden te vinden.

De vraag die in dit proefschrift centraal staat is: heeft niet-invasieve hersenstimulatie een positief effect op stress-gerelateerde mentale gezondheid bij militairen en veteranen? Het onderzoek is daarbij specifiek gericht op transcraniële gelijkstroomstimulatie, ofwel tDCS (*transcranial direct current stimulation*).

WAT IS TDCS?

Met behulp van tDCS beoogt men de prikkelbaarheid en activiteit van hersencellen te beïnvloeden. Twee of meerdere elektroden worden op het hoofd gelegd. Daartussen wordt een zwakke gelijkstroom gestuurd van 1 tot 2 milliampère. Een deel van de stroom bereikt de hersenen en verspreidt zich over het buitenste deel van de hersenschors. Studies naar het effect van tDCS laten het volgende beeld zien: de elektrische stroom zorgt in het bereikte deel van de hersenschors voor een kleine verandering in de rustpotentiaal van neuronen. Dit kan de neurale cellen niet direct activeren, maar zorgt er wel voor dat de kans op een actiepotentiaal toeneemt of afneemt. Hierdoor kunnen cellen makkelijker of juist minder makkelijk vuren. Om specifieker te zijn: onder de positieve elektrode (anode) heeft het elektrische veld een inwaartse stroomrichting. Dit zorgt ervoor dat neuronen makkelijker kunnen vuren en makkelijker signalen naar elkaar kunnen overdragen via synaptische verbindingen. Onder de

negatieve elektrode (kathode) heeft het elektrische veld een uitwaartse stroomrichting. Dit verlaagt de neurale prikkelbaarheid juist en kan signaaloverdracht afremmen.

Naast tDCS is transcraniële magnetische stimulatie (TMS) een bekende vorm van niet-invasieve hersenstimulatie. TMS werkt op basis van magnetische pulsen. In tegenstelling tot tDCS, kunnen TMS-pulsen wel direct actiepotentialen opwekken of juist onderdrukken. Echter heeft tDCS ten opzichte van TMS een aantal praktische en economische voordelen: tDCS heeft een gunstiger veiligheidsprofiel, is goedkoper, eenvoudiger te gebruiken, en draagbaar. Deze eigenschappen van tDCS kunnen voordelen bieden voor gebruik binnen de militair-operationele context en binnen de poliklinische context.

WAAROM TDCS BIJ STRESS EN MENTALE GEZONDHEIDSKLACHTEN?

Stress-gerelateerde mentale gezondheidsklachten worden in verband gebracht met een ontregeling in de prefrontale hersenschors (PFC). De PFC speelt een belangrijke rol in het reguleren van emoties, gedachten en gedrag. Functionele hersenscans hebben laten zien dat tijdens het reguleren van gevoelens van angst of boosheid de laterale (buitenste) gebieden van de PFC minder actief zijn bij patiënten met PTSS in vergelijking met gezonde controles. Activiteit in deze PFC-gebieden zou kunnen worden gestimuleerd met behulp van anodale tDCS. Op die manier zou tDCS een positief effect kunnen hebben op herstel of preventie van stress-gerelateerde mentale gezondheidsklachten.

WAT IS ER IN DIT PROEFSCHRIFT ONDERZOCHT EN GEVONDEN?

Analyse van eerdere bevindingen

Hoofdstuk 2 beschrijft een systematische review en meta-analyse die werd uitgevoerd om meer inzicht te krijgen in effecten van niet-invasieve hersenstimulatie van de PFC. In eerdere tDCS- en TMS-studies is daarbij vaak gekeken naar emotionele reactiviteit. Emotionele reactiviteit is de mate waarin negatieve emoties worden ervaren in reactie op stress. Dit speelt een rol in stress-gerelateerde mentale gezondheidsklachten. Emotionele reactiviteit wordt vaak gekwantificeerd door de intensiteit van emotionele ervaringen te meten in reactie op een stressmanipulatie. Stressmanipulaties bestaan bijvoorbeeld uit het tonen van emotioneel schokkende afbeeldingen of video's, of het uitvoeren van een stressvolle taak. Op het moment van deze studie waren de meeste tDCS- en TMS-onderzoeken naar emotionele reactiviteit uitgevoerd bij gezonde vrijwilligers, waarbij metingen werden gedaan tijdens of na één enkele hersenstimulatiesessie van tien tot dertig minuten.

De resultaten van **hoofdstuk 2** laten zien dat binnen dit domein slechts een klein aantal studies met TMS is uitgevoerd. Deze TMS-studies verschilden bovendien sterk in de gebruikte stimulatie-instellingen. Het is daarom wellicht niet verrassend dat de resultaten sterk varieerden tussen de individuele TMS-onderzoeken, en dat alle TMS-onderzoeksresultaten samen geen eenduidig effect op emotionele reactiviteit lieten zien. De resultaten van het grotere aantal tDCS-studies binnen dit domein varieerden ook tussen de onderzoeken, maar

de meta-analyse van alle tDCS-studies samen toonde aan met een klein maar statistisch significant effect dat tDCS emotionele reactiviteit kan verlagen. Dit effect werd gevonden ongeacht of de PFC in de linker of rechter hersenhelft was gestimuleerd, maar was alleen significant bij toepassingen van *anodale* tDCS op de PFC. Deze resultaten ondersteunden het idee om de klinische toepassing van anodale tDCS bij stress-gerelateerde mentale gezondheidsklachten verder te onderzoeken.

De vertaling naar de (klinische) praktijk

De twee experimentele interventiestudies van dit proefschrift zijn beschreven in de **hoofdstukken 3** tot **6.** In deze studies is de vertaling gemaakt van onderzoeken in een laboratorium-setting, zoals de onderzoeken die staan beschreven in **hoofdstuk 2**, naar onderzoeken met een toepassing voor stress-gerelateerde mentale gezondheid van militairen en veteranen. Daarbij werd een idee uit de zogenaamde '*activity-selective*' hypothese gevolgd. Deze hypothese stelt dat tDCS meer effect heeft op neuronen en synaptische verbindingen die actief bezig zijn met informatieverwerking tijdens de stimulatie. Overeenkomstig deze hypothese lieten een aantal studieresultaten uit **hoofdstuk 2** inderdaad zien dat het effect van tDCS op emotionele reactiviteit sterker was wanneer iemand actief bezig was met emotieregulatie. Daarom werd in beide interventiestudies tDCS gecombineerd met een cognitieve oefening op een computertaak.

Hoofdstuk 3 beschrijft de eerste interventiestudie die is uitgevoerd onder honderd militairen en veteranen die in behandeling waren voor PTSS, een angststoornis of agressieregulatie-problemen. Volgens eerder onderzoek hebben mensen met deze klachten een verminderd vermogen om impulsieve of ongepaste emoties en reacties in te houden of af te remmen. Dit wordt ook wel verminderde inhibitiecontrole genoemd. De tDCS-interventie in deze studie was daarom gericht op het bevorderen van inhibitiecontrole. In de hersenen is inhibitiecontrole gerelateerd aan activiteit in een PFC-gebied in de rechterhersenhelft, namelijk de inferieure frontale gyrus (IFG). De hypothese was daarom dat stimulatie van de rechter IFG met anodale tDCS inhibitiecontrole zou versterken, en via die weg herstel van klachten zou bevorderen.

In deze studie werd de rechter IFG herhaaldelijk gestimuleerd, namelijk in vijf tDCS-sessies verspreid over twee of drie weken. Deelnemers ontvingen tDCS met een stroomsterkte van 1.25 milliampère gedurende 20 minuten per sessie. Tijdens tDCS trainden deelnemers hun inhibitiecontrole met behulp van de zogenaamde 'Stop-Signaal-taak' op de computer. Inhibitiecontrole werd voorafgaand en na afloop van de tDCS-trainingsinterventie gemeten met andere computertaken (de Go/No-go-taak en de Impliciete-Associaties-taak). Vragenlijsten werden gebruikt om klachtenniveaus te meten vóór en na de tDCS-interventie, na drie maanden en na een jaar. Het onderzoek werd placebo-gecontroleerd uitgevoerd. Dat wil zeggen dat actieve tDCS werd toegepast bij de ene helft van de deelnemers, terwijl de andere helft *sham* tDCS ontving. Bij *sham* tDCS gaat de elektrische stimulator al na een paar seconden langzaam uit waardoor er geen actieve stimulatie van de hersenschors plaatsvindt.

In tegenstelling tot wat we verwachtten, werden er geen significante verschillen gevonden tussen de groepen die actieve tDCS of *sham* tDCS hadden ontvangen. Dat wil zeggen dat deelnemers uit de actieve tDCS groep niet beter presteerden dan de *sham* tDCS groep op de inhibitiecontroletaak tijdens de tDCS-sessies, noch op de andere inhibitiecontroletaken. Eveneens werden geen significante groepsverschillen gevonden in klachtenniveaus direct na de interventie, na drie maanden of na een jaar. Deze studie liet dus geen bewijs zien voor effecten van de gecombineerde tDCS-trainingsinterventie zoals hier toegepast op inhibitiecontrole of op stress-gerelateerde mentale gezondheidsklachten bij militairen en veteranen.

Hoofdstuk 4 beschrijft een kwalitatief onderzoek dat grotendeels is gebaseerd op interviews met zeven militaire patiënten en vijf behandelaren van de militaire geestelijke gezondheidszorg. Dit onderzoek is uitgevoerd naast het kwantitatieve onderzoek van **hoofdstuk 3**. De aanleiding voor deze studie was dat een succesvolle implementatie van potentiële nieuwe behandelmethoden zoals tDCS niet alleen afhangt van de effectiviteit, maar ook van hoe aanvaardbaar de methode is voor de gebruikers.

Uit de interviews kwam naar voren dat zowel de patiënten als behandelaren positief waren over tDCS als mogelijke neurobiologische *add-on* behandelmethode die kan worden toegevoegd aan psychologische behandeling. Zowel patiënten als behandelaren benoemden echter wel dat begrip van het werkingsmechanisme van tDCS beperkt was gebleven, terwijl begrip als belangrijk werd ervaren voor de aanvaardbaarheid van tDCS. Dit onderstreept het belang van passende informatieverstrekking over onderzoeksinterventies en nieuwe behandelmethoden binnen de geestelijke gezondheidszorg. Bij tDCS als behandeltechniek werden geen specifieke nadelen ervaren, behalve de frequente bezoeken voor tDCS-sessies in het behandelcentrum. Dit benadrukt het voordeel van tDCS vanwege de mogelijkheid tot schaalbare toepassingen, bijvoorbeeld vanuit huis.

Hoofdstukken 5 en **6** beschrijven de tweede interventiestudie met tDCS die werd uitgevoerd onder 79 militairen zonder mentale gezondheidsklachten. De studie was gericht op het versterken van het vermogen om stress en emoties te reguleren. Adequate regulatie van stress en emoties is zowel belangrijk bij operationeel functioneren in stressvolle omstandigheden, als bij de preventie van mentale gezondheidsklachten. Bij emotieregulatie speelt het werkgeheugen een belangrijke rol. In het werkgeheugen komt informatie binnen en wordt tijdelijk vastgehouden of verwerkt. Ook emotionele informatie kan op die manier tijdelijk worden vastgehouden en verwerkt, bijvoorbeeld om een passende interpretatie van of reactie op een stressvolle gebeurtenis te vinden. In de hersenen zijn werkgeheugen en emotieregulatie sterk gerelateerd aan activiteit in de dorsolaterale PFC (DLPFC). Op grond hiervan was de hypothese dat stimulatie van de rechter DLPFC met anodale tDCS werkgeheugencapaciteit zou verhogen. Dit zou vervolgens emotieregulatie kunnen verbeteren.

In deze studie werd de rechter DLPFC herhaaldelijk gestimuleerd, namelijk in drie tDCS-sessies verspreid over één of twee weken. Deelnemers ontvingen tDCS met een stroomsterkte van 2.0 milliampère gedurende 20 minuten per sessie. Tijdens tDCS trainden deelnemers hun werkgeheugen met behulp van de zogenaamde '*N-Back'*-taak op de computer. Voorafgaand en na afloop van de tDCS-trainingsinterventie werd emotieregulatie gemeten met behulp van een zogenaamde '*threat-of-shock'*-taak. Hierbij worden onvoorspelbare aversieve elektrische stroomschokken toegediend op de arm van een deelnemer. De mate waarin deelnemers hun angst of spanning voor de elektrische schokken konden reguleren werd gekwantificeerd door fysiologische schrikreacties (de oogknipperreflex) en emotionele ervaringen te meten tijdens de taak. Ook deze studie werd placebo-gecontroleerd uitgevoerd: de helft van de deelnemers kreeg actieve tDCS, terwijl de andere helft *sham* tDCS onderging.

Zoals beschreven in **hoofdstuk 5**, werden er in tegenstelling tot onze hypothese geen significante verschillen gevonden tussen de groepen die actieve tDCS of *sham* tDCS hadden gehad. Dat wil zeggen: deelnemers uit de actieve tDCS groep presteerden niet beter dan de controlegroep op de werkgeheugentaak tijdens de tDCS-sessies of tijdens de nameting. Eveneens werden geen significante effecten van tDCS gevonden op fysiologische en emotionele reacties tijdens de threat-of-shock taak. Deze resultaten bieden geen ondersteuning voor een effect van de tDCS-trainingsinterventie op het werkgeheugen en emotieregulatie. Opvallend genoeg werden er wel groepsverschillen gevonden in een exploratieve, post-hoc analyse. Deze analyse werd gedaan om de invloed van individuele eigenschappen op de effectiviteit van tDCS in kaart te brengen. Zo werden onder andere de invloed van leeftijd en van individuele verschillen in hersenactiviteit bekeken. Op het gebied van hersenactiviteit werd specifiek gekeken naar de EEG theta/beta power ratio. De theta/beta power ratio is eerder in verband gebracht met emotioneel-gedreven gedrag en emotieregulatie, en wordt afgeleid van hersenfilmpjes die tijdens rust worden gemaakt in de frequenties van 4-7 Hz (theta) en van 13-30 Hz (beta). De exploratieve analyseresultaten lieten zien dat actieve tDCS de werkgeheugenprestaties significant verbeterde ten opzichte van *sham* tDCS, maar alleen naarmate iemand een lagere leeftijd of een hogere theta/beta power ratio had. Dit effect was alleen aanwezig tijdens de eerste tDCS-trainingssessie.

Hoofdstuk 6 beschrijft de uitkomsten van deze studie die zojuist is beschreven op andere cognitieve processen die betrokken zijn bij het reguleren van stress en emotioneel gedrag. Daarbij werd inhibitiecontrole gemeten op basis van taakpresentaties (de *Go/No-go*-taak), en in hersenactiviteit op basis van EEG *event-related potentials* (de N2 en P3 golf). Daarnaast is inhibitiecontrole samen met vermijding en angst eerder in verband gebracht met relatief actievere PFC in de rechterhersenhelft ten opzichte van de linkerhersenhelft. Deze PFC-asymmetrie werd gekwantificeerd op basis van alfa-oscillaties in het EEG tijdens rust. Ten slotte werd aandachtscontrole gemeten met een zelf-rapportagevragenlijst.

De resultaten lieten geen significante verschillen zien tussen de actieve tDCS en *sham* tDCS groep. De resultaten van **hoofdstuk 6** komen daarmee overeen met de resultaten

van **hoofdstuk 5**, en suggereren dat de gecombineerde tDCS-trainingsinterventie zoals hier toegepast geen groepsgewijze effecten had op inhibitie- of aandachtscontrole, of op gerelateerde elektrofysiologische processen in de hersenen.

SLOTBESCHOUWINGEN

TDCS kan een klein positief effect hebben op specifieke cognitieve prestaties, zoals beschreven in **hoofstukken 2** en **5.** Echter, over het geheel genomen laten de studieresultaten van dit proefschrift geen overtuigend bewijs zien dat stimulatie van de PFC met anodale tDCS een positief effect heeft op het reguleren van stress en emoties, of op cognitieve processen die daarbij betrokken zijn. Dit suggereert dat tDCS zoals het in deze studies is toegepast geen toegevoegde waarde heeft voor het bevorderen van mentale gezondheid bij militairen en veteranen.

EEN KRITISCHE TERUGBLIK

Een kritische evaluatie van de studies laat zien dat er sterke en zwakke aspecten zijn in de manier waarop hersenstimulatie in dit proefschrift is toegepast en waarop de uitkomsten zijn gemeten. Enerzijds hebben we in onze studies een belangrijke vertaalslag gemaakt van experimentele tDCS-studies in gezonde vrijwilligers met veelal kleine steekproeven, naar klinisch relevante tDCS-studies in de militaire doelgroep. De studies hadden grote steekproeven, gerandomiseerde en placebo-gecontroleerde designs, en uitkomstmaten op verschillende niveaus, inclusief neurofysiologie, gedrag en subjectieve emotionele ervaringen.

Anderzijds is er nog veel onbekend over het werkingsmechanisme van tDCS, en over gezonde en pathologische hersenprocessen bij angst en stress. Om een voorbeeld te geven: het verhogen van neurale prikkelbaarheid in PFC-gebieden lijkt gunstig te zijn om adequate emotieregulatie faciliteren. Echter, dezelfde PFC-gebieden zijn ook betrokken bij excessief piekeren. Bovendien is er nog veel onduidelijk over hoe tDCS de neurale activiteit in de PFC precies beïnvloedt, en hoe dit zich vertaalt naar gedrag en symptomen. Complexe interacties tussen verschillende neuronen en verschillende hersennetwerken zorgen ervoor dat 'meer' neurale prikkelbaarheid in een hersengebied niet automatisch 'meer' van een bepaald gedrag betekent. Daarnaast zijn er veel factoren die het effect van hersenstimulatie op gedrag beïnvloeden. Niet alleen de instellingen van het stimulatieprotocol zoals duur en intensiteit bepalen de uitkomst van de stimulatie, maar ook iemands individuele eigenschappen en de toestand waarin iemand verkeert. Over de invloed van deze factoren is nog veel onbekend, en de veelheid aan factoren kan het vinden van het juiste stimulatieprotocol een complexe en intensieve zoektocht maken. In de discussie van dit proefschrift (**hoofdstuk 7**) wordt betoogd dat dit soort ontbrekende stukjes kennis er wellicht voor gezorgd hebben dat veel tDCS-studies, waaronder de onze, (nog) niet het beoogde effect opleveren.

SUGGESTIES VOOR TOEKOMSTIG ONDERZOEK

Toekomstig onderzoek naar niet-invasieve hersenstimulatie zou zich bijvoorbeeld meer kunnen richten op de samenwerking tussen verschillende hersengebieden, in plaats van te focussen op één hersengebied. Kennis omtrent samenwerking tussen verschillende hersengebieden kan helpen om te bepalen wat het optimale hersengebied is om tDCS op toe te passen, of om een beter beeld te krijgen of hersenstimulatie bij iemand effectief zal zijn. Dit idee stemt onder andere overeen met de exploratieve resultaten van **hoofdstuk 5** die laten zien dat de EEG theta/beta power ratio voorspelt in hoeverre tDCS effect heeft op werkgeheugenprestaties. Nog beter zou het zijn als hersenstimulatie beter aansluit bij de interactie tussen hersengebieden. Transcraniële wisselstroomstimulatie biedt een mogelijke manier om activiteit tussen hersengebieden beter op elkaar af te stemmen of te synchroniseren. Synchronisatie tussen de PFC en hippocampus is bijvoorbeeld belangrijk bij geheugenprocessen die een essentiële rol spelen bij exposure-behandeling voor angst en PTSS.

TDCS IN DE PRAKTIJK?

De resultaten van dit proefschrift en de onzekerheden rondom de effecten van tDCS suggereren dat deze techniek nog niet geschikt is voor de klinische toepassing. Op het gebied van stress-gerelateerde mentale gezondheid bij militairen bestaan er echter wel andere niet-invasieve hersenstimulatietechnieken die meer potentie hebben. Ten eerste zijn er in recente onderzoeken positieve effecten van TMS gevonden in de behandeling van PTSS. Ook biedt, zoals hierboven geopperd, transcraniële wisselstroomstimulatie nieuwe mogelijke toepassingen. Toekomstig onderzoek moet de uiteindelijke klinische potentie uitwijzen van niet-invasieve hersenstimulatietechnieken voor de preventie en behandeling van stress-gerelateerde mentale gezondheid onder militairen en veteranen.

A

LEKENSAMENVATTING

Het is bekend dat stress en trauma kunnen zorgen voor psychische klachten, en dat bij deze psychische klachten bepaalde hersengebieden afwijkende activiteit laten zien. Het beïnvloeden van die hersenactiviteit zou preventie en behandeling van psychische klachten kunnen bevorderen, in het bijzonder bij militairen en veteranen. Voor hen namelijk blijken gangbare therapieën vaak onvoldoende effectief.

Hersenactiviteit kan op een veilige manier worden beïnvloed met niet-invasieve hersenstimulatie. Het onderzoek in dit proefschrift is gericht op een specifieke hersenstimulatietechniek die wordt aangeduid met '*tDCS*', een afkorting van *transcranial direct current stimulation*. Eerder onderzoek naar hersenstimulatie met tDCS bij gezonde vrijwilligers toont aan dat tDCS emotionele en cognitieve processen kan beïnvloeden in een gecontroleerde testkameromgeving. In dit proefschrift is een vertaling gemaakt van dat onderzoek naar effecten op stress-gerelateerde mentale gezondheid bij militairen en veteranen.

De studieresultaten in dit proefschrift leveren geen overtuigend bewijs voor positieve effecten van tDCS op emotionele controle of herstel van klachten bij militairen en veteranen. Dat wil zeggen: we vonden geen relevante effecten van de specifieke manier waarop tDCS in dit onderzoek is toegepast in twee placebo-gecontroleerde interventiestudies onder militairen en veteranen met angst, agressie- of posttraumatische stressklachten, en onder militairen zonder mentale gezondheidsklachten. Onze bevindingen suggereren dat hersenstimulatie met tDCS nog niet geschikt is om mentale gezondheid van militairen en veteranen te bevorderen, en onderstrepen het belang van verder onderzoek naar het werkingsmechanisme van tDCS en de juiste toepassingen ervan.

LAY SUMMARY

It is known that stress and trauma can cause psychological complaints, and that these psychological complaints are accompanied by abnormal activity in certain brain areas. Influencing this brain activity could promote the prevention and treatment of psychological complaints, particularly among military personnel and veterans. For them, current therapies are often insufficiently effective.

Brain activity can be influenced in a safe way with non-invasive brain stimulation. The research in this dissertation focuses on a specific brain stimulation technique called '*tDCS*', an abbreviation of *transcranial direct current stimulation*. Previous research on brain stimulation with tDCS in healthy volunteers shows that tDCS can affect emotional and cognitive processes in a controlled test room environment. This dissertation translated that research into effects on stress-related mental health in military personnel and veterans.

The study results in this dissertation do not provide convincing evidence for positive effects of tDCS on emotional control or recovery from symptoms in military personnel and veterans. That is, we found no relevant effects of the specific way tDCS was applied in two placebo-controlled intervention studies among military personnel and veterans with anxiety, aggression or post-traumatic stress symptoms, and among military personnel without mental health symptoms. Our findings suggest that brain stimulation with tDCS is not yet ready for use in the context of mental health in military personnel and veterans, and underscore the importance of further research into the mechanism of action of tDCS and effective applications.

LIST OF PUBLICATIONS

PEER REVIEWED PUBLICATIONS:

Smits, F.M., Schutter, D.J.L.G., van Honk, J., & Geuze, E. (2020). Does non-invasive brain stimulation modulate emotional stress reactivity?. *Social Cognitive and Affective Neuroscience*, *15*(1), 23-51.

Smits, F.M., Geuze, E., Schutter, D.J.L.G., van Honk, J., & Gladwin, T.E. (2021). Effects of tDCS during inhibitory control training on performance and PTSD, aggression and anxiety symptoms: a randomized-controlled trial in a military sample. *Psychological medicine*, 1-11.

Smits, F.M.*, de Kort, G.J.*, & Geuze, E. (2021). Acceptability of tDCS in treating stress-related mental health disorders: a mixed methods study among military patients and caregivers. *BMC psychiatry*, *21*(1), 1-12.

Smits, F.M.*, Porcaro, C.*, Cottone, C., Cancelli, A., Rossini, P.M., & Tecchio, F. (2016). Electroencephalographic fractal dimension in healthy ageing and Alzheimer's disease. *PloS one*, *11*(2), e0149587.

Tecchio, F., Cancelli, A., Cottone, C., Ferrucci, R., Vergari, M., Zito, G., Pasqualetti, P., Filippi, M.M, Ghazaryan, A., Lupoi, D., **Smits, F.M.**, Giordani, A., Migliore, S., Porcaro, C., Salustri, C., Rossini, P.M., & Priori, A. (2015). Brain plasticity effects of neuromodulation against multiple sclerosis fatigue. *Frontiers in neurology*, *6*, 141.

* These authors contributed equally to this work.

MANUSCRIPTS ACCEPTED FOR PUBLICATION:

Smits, F.M., Geuze, E., de Kort, G.J., Kouwer, K., Geerlings, L., van Honk, J., & Schutter, D.J.L.G. Effects of multisession transcranial direct current stimulation on stress regulation and emotional working memory: a randomized controlled trial in healthy military personnel. *Neuromodulation: Technology at the Neural Interface*. (Accepted for publication)

CURRICULUM VITAE

ENGLISH

Fenne Smits was born on September 25th 1992 in Pijnacker, the Netherlands. Fenne attended the Beatrixschool in Pijnacker and completed VWO at the Christelijk Lyceum Delft. In 2010 she started a Bachelor Psychology at Leiden University, followed by the Research Master Brain and Cognitive Sciences at the University of Amsterdam in 2013. Fenne's interest was drawn to the brain and its link to healthy and pathological behavior. Her research internships focused on structural and functional brain alterations related to psychiatric and neurological diseases, with a specific focus on patients with major depression (Academical medical Center Amsterdam, under supervision of dr. Roel Mocking) and Alzheimer patients (Institute for Cognitive Sciences and Technologies (ISTC-CNR) in Rome, Italy, under supervision of dr. Franca Tecchio). In the meanwhile, Fenne worked as a research assistant at the Center for Human Drug Research in Leiden. At dr. Franca Tecchio's lab, Fenne became enthusiastic about non-invasive brain stimulation in a research project with multiple sclerosis patients. After obtaining her Master's degree in 2015, Fenne started working at the Brain Research and Innovation Centre of the Dutch Ministry of Defence, in collaboration with the Psychiatry Department of the University Medical Center Utrecht. Here, she implemented her interest in brain stimulation and carried out the research that resulted this dissertation. After finishing her PhD, Fenne continues to work as a post-doctoral researcher within the Brain Research and Innovation Centre, in close collaboration with Prof. dr. Dennis Schutter's lab at the Experimental Psychology department of Utrecht University.

NEDERLANDS

Fenne Smits is geboren op 25 september 1992 in Pijnacker, Nederland. Fenne zat op de Beatrixschool in Pijnacker en heeft VWO gedaan op het Christelijk Lyceum Delft. In 2010 startte ze met de Bachelor Psychologie aan de Universiteit Leiden, gevolgd door de Research Master Brain and Cognitive Sciences aan de Universiteit van Amsterdam in 2013. Fenne's interesse ging uit naar het brein en de link met gezond en pathologisch gedrag. Haar onderzoeksstages richtten zich op structurele en functionele veranderingen in de hersenen gerelateerd aan psychiatrische en neurologische aandoeningen, met een specifieke focus op patiënten met depressie (Academisch Medisch Centrum Amsterdam, onder supervisie van dr. Roel Mocking) en Alzheimerpatiënten (Institute for Cognitive Sciences and Technologies (ISTC-CNR) in Rome, Italië, onder supervisie van dr. Franca Tecchio). In de tussentijd werkte Fenne als onderzoeksassistent bij het Center for Human Drug Research in Leiden. In het lab van dr. Franca Tecchio werd Fenne enthousiast over niet-invasieve hersenstimulatie in een onderzoeksproject met multiple sclerose patiënten. Na het behalen van haar masterdiploma in 2015 is Fenne gaan werken bij het Expertisecentrum van de Militaire GGZ, in samenwerking met de afdeling Psychiatrie van het Universitair Medisch Centrum Utrecht. Hier gaf ze invulling aan haar interesse in hersenstimulatie en voerde ze het onderzoek uit dat resulteerde in dit proefschrift. Na het afronden van haar promotie werkt Fenne verder als postdoctoraal onderzoeker binnen het Expertisecentrum van de Militaire GGZ, in nauwe samenwerking met het lab van Prof. dr. Dennis Schutter bij de afdeling Psychologische Functieleer van de Universiteit Utrecht.

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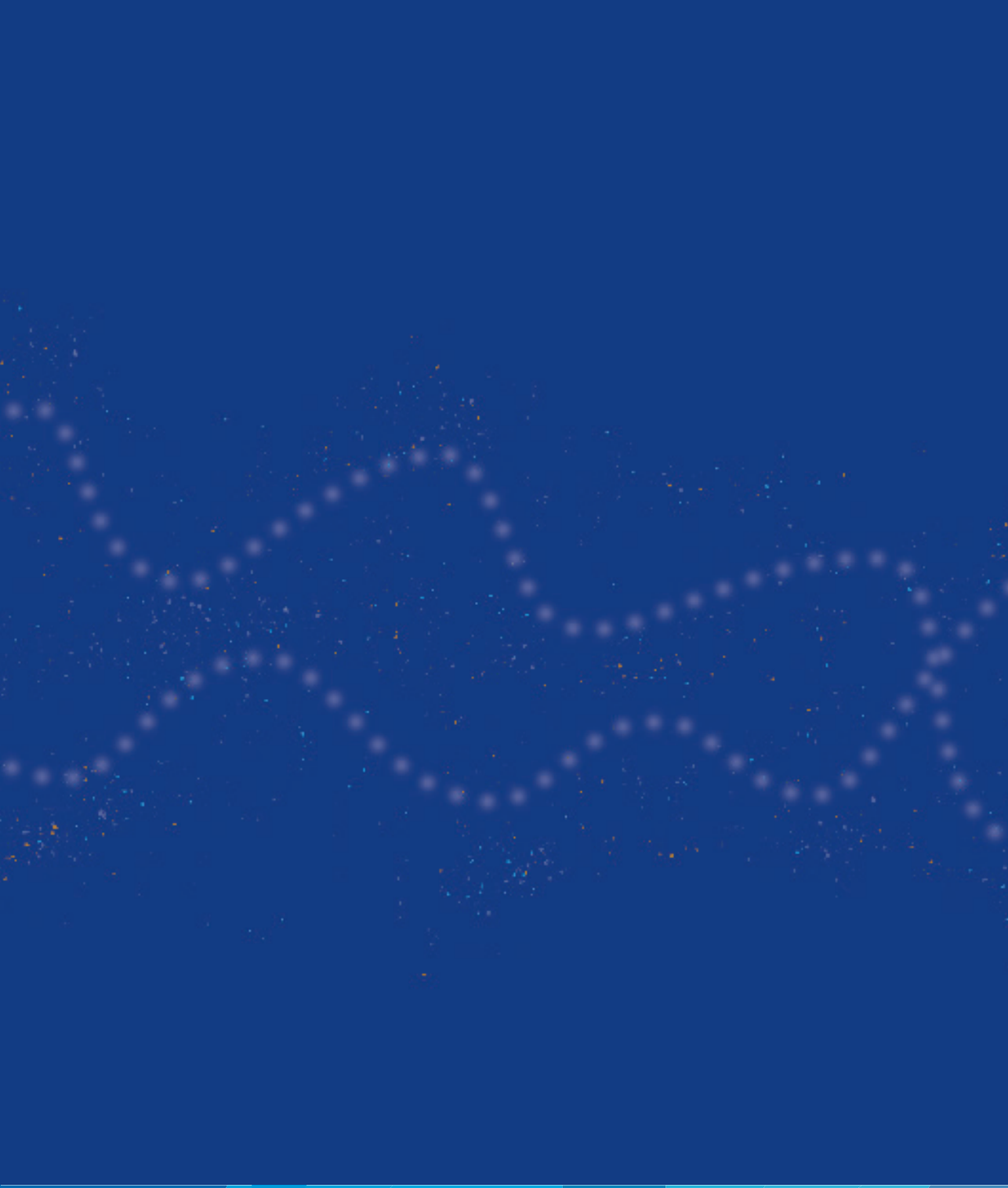

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